HUMAN GASTRIC FUNCTION

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An Experimental Study of a Man and His Stomach

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Foreword

EVERY man has a stomach, unless, to prolong life, the surgeon has been allowed to remove it Only relatively few men, because of accident or disease, have been compelled to live with their stomachs opened and connected with the surface of the body—a condition which allows investigators to look in, to sample the gastric juices and the partially digested food, and to apply revealing tests in order to increase knowledge of the digestive process Hitherto in the United States there have been two famous cases of this nature Beaumont's cantankerous Alexis St M, and Carlson's Fred V As mentioned in Chapter I, there have been other human instances of gastric fistula that have been studied incidentally and for particular interests I venture to declare, however, that the functions of the stomach have never been investigated with the detailed care, the skill and ingenuity that have been displayed in the researches carried out by the authors of this volume on the present subject, Tom Not only the natural activities of the organ—its secretions and motions and associated variations of blood flow, its responses to different stimuli and its effects on various foodstuffs—but also the influence of many agents commonly employed to alter these functions have been critically

examined in the favorable circumstances which Tom presented

Perhaps most illuminating of all the observations are those on the intimate relations between emotional states and gastric activity In that respect the investigators were fortunate, for the subject was a sensitive, proud, and independent individual, at different times anxious, fearful, difficult, and obstinately decisive He had an emotional range and responsiveness that permitted nice discriminations which the authors have fully utilized The interesting fact that frustration and repressed conflict were associated with hyperemia and with increase of motility and secretion will come as a surprise to many Likewise highly significant is evidence that engorgement of the mucosa, whatever its cause, is associated with lessened resistance to trauma, for as the authors point out, this condition has importance in explaining the incidence of gastric ulcer Obviously the extent and variety of testimony here accumulated provides interest not only for clinicians but for physiologists, pharmacologists, psychiatrists, and pathologists, as well

Such thorough examination of a single individual may be criticized as not offering a basis for broad generalizations There may be, admittedly, some individual peculiarities which would not permit the features of this one man and his stomach to be applied to all men and their stomachs Nevertheless, the general normality of Tom is favorable to his being a good exemplar of his fellows However one may regard the bearing of this case on other cases it is clear that the admirably specific and exact and critical examination of the numerous aspects of gastric physiology and pathology, here presented, offers a challenge to others who may wish to attempt similar studies on other individuals normal or pathological

Much value has come to medical science and practice from

a mutual influence of the laboratory and the clinic on one another Suggestions from facts noted in the clinic can be taken to the laboratory and there analyzed under experimental conditions often impossible in research on human beings The results from investigations on lower animals may in turn be helpful and illuminating for further clinical testing Experimenters having laboratory facilities—physiologists pathologists, pharmacologists, and others—will find in this report many hints for further work

All whose interests are served by the important contributions to knowledge contained in this volume owe a tribute of appreciation not only to the investigators, who ingeniously devised the methods and made the careful observations described in the following pages, but also to Tom, who faithfully collaborated with them

WALTER B CANNON

Preface

THIS book is not primarily the description of a 'rare case' It aims to be a simple statement of the workings of the human stomach It was made possible through 'Tom, who was generous enough to allow a tragic accident to himself to become the basis of a new approach to essential questions concerning the stomach

We are fortunate to live in a day when tools and concepts can be fashioned for dealing with an organ in the setting of the daily experience of the man Thus for the first time, an evaluation of circulatory changes in the gastric and duodenal mucosa has been possible The wide variations in blood flow and their relation to secretion and contractility have been found to have dramatic implications for health and disease

To Doctor Walter B Cannon goes our gratitude for his wise advice and discriminating criticism

We wish to express our thanks to Isabel Bishop Helen Goodell Margaret Scharf Lillian Riblet and Margaret Meixner, who helped with the technical work the preparation of the manuscript and correction of proofs We also gratefully acknowledge the suggestions and criticism of our colleagues in the Departments of Medicine Psychiatry, Physiology, Biochemistry, Anatomy and Pharmacology

The studies included in this monograph were supported by funds from the New York Hospital and the Departments of Medicine and Psychiatry, Cornell University Medical College, and a grant from the Josiah Macy, Jr , Foundation They were undertaken during the tenure by one of us (S W) of a National Research Council fellowship in the Medical Sciences

Permission to reproduce charts and data contained in articles in the Journal of the American Medical Association, the Journal of Clinical Investigation, the American Journal of Physiology, the American Journal of Digestive Diseases, the Proceedings of the Association for Research in Nervous and Mental Diseases, and the Transactions of the Association of American Physicians has been kindly accorded by the publishers of these journals and volumes

S W
H G W

New York Hospital

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Introduction

ONE hundred years ago Beaumont[1] wrote 'I have availed myself of the opportunity afforded by a concurrence of circumstances which probably never can again occur ' It is true that the precise series of events which resulted in a permanent opening into the stomach of Alexis St Martin has probably not been repeated, but Beaumont's opportunity to study the physiology of the stomach at close range through a gastric fistula has not remained unique

During the succeeding years, while others have had patients with holes in their stomachs to study, there has been only one investigation which has compared in scope with Beaumont's work,[2] namely, Carlson's study of Mr V By virtue of new approaches to the study from one generation to the next, however, additional facts have been learned and various aspects of the problem of gastric function have been clarified The problems could never be disposed of by a single worker, however ideal his opportunities for the questions put to nature vary from one generation to the next An investigator's horizon is limited by the height of the vantage point on which he stands These vantage points are the prevailing concepts of the day Few men have been able to look beyond the horizon of their generation

Beaumont's work was influenced by the widespread interest in inorganic chemistry which prevailed in his day Therefore, in his studies on Alexis St Martin he was principally concerned with discerning the processes involved in converting a bolus of food into an amorphous, semi-fluid chyme He interested himself primarily in the gastric juice, and this he emphasized in the title of his treatise 'Experiments and Observations on the Gastric Juice and the Physiology of Digestion' The critics of Beaumont's day, too, were preoccupied with the same considerations, and they were disappointed by his failure to show whether or not there was a 'vital force' in the stomach which enabled food to be chymified more readily in vivo than when incubated with gastric juice in vitro[3]

Richet's[4] observations on an early gastrostomy patient were made about fifty years after Beaumont's publication His interests were mainly limited to the chemistry and physiological properties of gastric juice, although he did explore the sensibility of the gastric mucosa

Carlson,[2] twenty-five years after Richet, also studied a subject with a hole in his stomach The passage of time had offered him a new approach to the investigation The star of 'vitalism' had faded, and 'mechanism' had taken its place A great school of physiologists had sprung up Their interests lay in the behavior of individual organs and in the mechanics of the interrelationships of organs Carlson's work was primarily concerned with kinetics The majority of his experiments on the stomach were directed towards a study of gastric motility and of 'hunger contractions in particular

A set of factors generally ignored by investigators included the influence of the circumstances surrounding an experiment on the function of the organ under observation This was true even after Pavlov had shown in dogs that the effects of envi-

ronmental situations to which the animals had learned to attach special significance manifested themselves in profound and prolonged alterations in gastric and salivary functions[5] He showed that the effects of these situational factors, like other biological phenomena were subject to analysis and to experimental approach Gradually there arose a fresh point of view, namely, to consider the stomach not as an isolated organ, but as a functioning unit in a whole integrated organism Much of the pioneering in this field was done by Cannon, whose studies showed that profound disturbances in gastric functioning occurred during emotional stress[6,7] The work of Cannon has had a broad influence on scientific thinking in America It is continually quoted by psychiatrists neurologists internists and physiologists Despite this, there is a general reluctance among investigators to apply the experimental method when studying the emotions

Beaumont Richet, and Carlson had all recognized that changes in gastric function occurred in association with varying emotional states, but they did not find it appropriate to make systematic observations upon them Neither did they seem to appreciate the magnitude of these changes and their possible relation to epigastric distress and disease The significance of psychosomatic relationships lay beyond their horizon It looms large on ours today Therefore, it seemed important to us to explore the possibility that serious structural changes in the gastrointestinal tract may occur as a result of prolonged functional disturbances

BIBLIOGRAPHY

1 Beaumont, W *Experiments and observations on the gastric juice and the physiology of digestion* F P Allen, Plattsburg 1833 p 6

2 Carlson A J 'Contributions to the physiology of the stomach' 1-23, Beginning in *Am J Physiol* 31 151, 1912
3 Condie, D F 'Beaumont on digestion,' *Am J Med Sci* 14 117, 1834
4 Richet C 'Des proprietes chimiques et physiologiques du suc gastrique chez l homme et les animaux,' Appendice *A Jour de l Anat et de la Physiol* 14 170, 1878
5 Pavlov, I *The work of the digestive glands,* English translation from the Russian by W H Thompson, C Griffin & Co, London 1910
6 Cannon W B 'The influence of emotional states on the functions of the alimentary canal' *Am J Med Sci* 137 480 1909
7 Cannon W B *Bodily changes in pain, hunger, fear and rage* D Appleton & Co, New York, 1929

CHAPTER I

The Appearance and Behavior of a Stomach after Forty-seven Years of Feeding through a Gastric Fistula

History of Our Subject, Tom The subject, Tom, a 57-year-old man of Irish stock, was brought to the New York Hospital in 1895 at the age of 9, with an oesophageal stricture that had resulted from drinking extremely hot clam chowder Attempts to dilate the oesophagus with bougies failed so a lumen was channeled with a urethrotome For a few days Tom could swallow food but the surgeon was unable to keep the lumen open with repeated passage of bougies and slowly it closed off again Finally it became necessary to perform a gastrostomy Accordingly, the anterior portion of the greater curvature of the stomach was brought out and sutured to the abdominal wall Before the operation was completed, however, Tom's condition suddenly became precarious and it was necessary to finish the operation hurriedly without attempting a plastic closure Tom recovered from the operation, but was left with a defect in his abdominal wall 3 5 cm in diameter, through which a collar of redundant gastric mucosa herniated

Thereafter, he fed himself through the artificial opening

He placed food in his mouth, chewed it and then spit it into an ordinary kitchen funnel with an attached rubber hose, which he inserted into his stoma Following the conclusion of the meal he covered his defect with gauze and bound up his abdomen tightly, leaving the dressing in place until his next meal The saliva secreted between meals he allowed to accumulate temporarily in the upper end of the oesophagus and then emptied it at convenient intervals throughout the day This reservoir held approximately 100 cc of fluid He ate an average diet with little meat, but took 4-5 cups of weak tea or coffee with each meal, feeding himself only twice a day at intervals of at least 5 hours He learned that this was the minimum time required for the digestion of most of his meals, and that in order to avoid spilling stomach contents he must wait until the organ was empty before eating again His reason for restricting meat was his discovery that 6-9 hours were required for its digestion Like Richet's[1] patient he noted that leafy vegetables remained in his stomach for a long time, often 10-12 hours Residual amounts of spinach were especially easily recognized Generally, he observed that liquid foods were digested more quickly than solid ones

Unlike Richet's patient, Tom consistently took the food into his mouth before placing it in his stomach Introducing it directly into his stomach failed to satisfy his appetite Following his original operation, when he was markedly underweight, feedings poured into his stomach by a nurse and later by his mother kept him but poorly nourished When, however at his own suggestion he began to feed himself by taking all of the food into his mouth before placing it into his stomach he gained satisfactorily

Throughout his 47 years of living with a gastrostomy he maintained a good appetite The sight or thought of delec-

table dishes called forth a normal flow of saliva Opposite experiences induced nausea and retching, which persisted until he allowed the contents of his stomach to escape through his fistula

He remained free from chronic gastrointestinal complaints, such as 'heart-burn,' epigastric distress, anorexia, flatulence, and diarrhea, except under special circumstances, which will be discussed later

He smoked a pipe in moderation, but rarely cigarettes Occasionally he drank beer with his meals, but usually not more than 3-4 bottles a week He liked to taste the first few swallows and then he poured the rest directly into his stoma He rarely indulged in spirits, because small amounts, which spilled in the manipulation of the funnel caused burning of the granulating skin in the immediate vicinity of the stoma

On one occasion eight years after operation, while playing football he fell on a fumbled ball and two other boys piled on top of him For the rest of the day he had a severe pain in the abdomen and anorexia, and he ate no dinner In the early hours of the following morning he was awakened by an excruciating pain throughout the lower portion of the abdomen and examining his stomach for the first time he found a large portion of his gastric mucosa protruding through his opening looking like a huge rose It was necessary to enlarge the fistulous opening surgically in order to reduce the herniation Since then he has had two or three such episodes In each he was able to tuck his stomach back in by hand Following reduction however, cramping pains in the hypogastrium regularly occurred and persisted for about two and one half hours

About 18 months before we first saw him while he was working as a sewer laborer he found that the movement in

volved in swinging a pick caused the dressing over the gastrostomy opening to excoriate the edges of the wound and induce bleeding Every night when he changed his dressing he found it soaked with blood Finally, he sought medical advice from Dr Florence T Donovan of Staten Island, who found numerous small buds of tissue around the periphery of his redundant mucosa and on its under surface These Dr Donovan resected in an ingenious operation Thereafter the patient's red blood cell count, which had decreased to an anemia of 2,000,000 red blood cells per cu mm and a haemoglobin of 6 gm which had resulted from the bleeding, quickly rose to normal values where they were maintained Subsequent to the operation he had only slight spotting of blood on his dressings from time to time

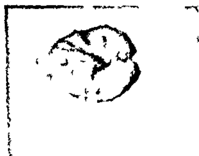
Appearance of the Subject Tom was a short man, barely 5 feet 4 inches tall, lithe, muscular, but slender, weighing 105 lbs He appeared about his age, 57 years His skin was of good texture and his tongue moist and pink with the usual number of papillae In the epigastrium midway between the xiphoid and umbilicus a defect was seen 3 5 cm in diameter, through which herniated a collar of gastric mucosa about 10 cm across (Fig 1) The underside of this collar presented the appearance of fibrous and granulating tissue The layer did not seem to be thick enough to contain much, if any, muscularis This impression gained support from the fact that no motor activity was observable in the prolapsed collar of stomach wall It was possible to replace nearly all of this tissue within the stomach cavity The line of attachment between skin and stomach was thus revealed This was tightly healed The 3-5 mm of skin immediately surrounding the defect was denuded, presenting a raw, granulating surface For a distance around the stoma of a 10 cm radius the skin





A View of patient reclining on laboratory table Note gastrostomy opening midway between umbilicus and xiphoid

B Funnel inserted into the stoma for feeding





C Close up of gastrostomy showing protruding collar of gastric mucosa

D Mucosa [illegible] back into the stomach exposing the underside of the protruding collar of mucosa and its junction with the skin





A Oblique chest film showing oesophageal occlusion with dilatation proximal to it outlined by barium.

B Antero posterior view of the stomach filled with barium Note forward rotation of greater curvature with direction of the pylorus posteriorly





C Right oblique view of the st mach showing the silhouette usually seen in anter p sterior view Note mall am unt of barium in duodenal cap

D hour film of the st mach (antero post) M t f the barium i in the small intestine

was pinker than normal, thin and parchment-like in consistency This layer could be displaced slightly over the deeper layers of the skin in a manner which suggested a blister There was, however, no accumulation of fluid beneath this loose skin The patient learned that this area of skin adjacent to his defect required meticulous care to protect it from maceration and digestion by the gastric juice

Radiographic Appearance of the Oesophagus and Stomach The oesophageal stricture and consequent dilatation above the stricture were demonstrated by x-ray (Fig 2) Fluoroscopic visualization while barium was poured in through the stoma * revealed an apparently normal rugal pattern The barium promptly passed through the pylorus and filled out the duodenal cap These structures as well as the duodenum and jejunum appeared entirely normal

The x-ray study illustrated well the method by which the gastrostomy was made The anterior aspect of the greater curvature of the stomach had been brought up to the abdominal wall, thus rotating the stomach on a horizontal axis and pointing the pylorus posteriorly The opening was then made into the stomach wall one third of the way from cardia to pylorus Representative views of the barium-filled stomach showing the duodenal cap and part of the small intestine appear in Fig 2 After two hours the stomach was nearly empty of barium

Appearance of the Mucous Membrane The character of our subject's defect offered an excellent opportunity for prolonged close inspection of the stomach mucosa by virtue of the large size of the defect and also because of the collar of mucous membrane which lay exposed on the abdominal wall The interior of the stomach was examined by means of an

* We are indebted to Dr Sidney Weintraub and the Department of Radiology for the radiographic interpretations.

regularly covered by a film of transparent mucus At times when its production appeared especially active, it became thick and opaque over certain areas and occasionally rolled up into small whitish flakes, which lay on the surface of the mucous membrane These precipitated bits of mucus were peeled away with some difficulty and were found to be insoluble in the gastric juice Their digestion was only partially effected after incubation with gastric juice for 24 hours It seems likely that they corresponded to the 'aphthous spots,' which Beaumont described in St Martin's stomach as 'white spots resembling coagulated lymph'

Secretion in the Stomach The appearance and consistency of the gastric juice varied widely from time to time, as did the concentration of acid in the specimens The latter ranged under differing circumstances from 10 to 120 clinical units A detailed study of the secretory function is presented in later chapters

Motor Activity When the barrel of the anoscope or any object larger than 5 cm in diameter was introduced through the stoma, the stomach wall closed in around it, grasped it, as it were, and milked it towards the pylorus It was necessary to inflate the organ with air in order to free the sides of the object introduced During inflation it was often possible to see wave-like indentations of the stomach At these times much of the air was forced through the pylorus, and abdominal distention resulted The distention persisted after the stomach was decompressed, and there occurred migratory cramps, which were felt over the whole abdomen At other times, the stomach wall appeared to be quiescent with no waves of contraction taking place

Plan of Study It was thought desirable to study these functions in more detail with the hope of clarifying the mechanisms

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B Antero posterior view of the stomach filled with barium Note forward rotation of greater curvature with direction of the pylorus posteriorly





C Right-oblique view of the stomach showing the silhouette usually seen in antero posterior view Note small amount of barium in duodenal cap

D 2 hour film of the stomach (antero-post) Most of the barium is in the small intestine

Fig.

area where the folds were absent and the mucosa velvety smooth There was, however, no other evidence of abnormality Detailed review of the operative procedures involved in the formation of the stoma and the passage of bougies in the oesophagus allowed the inference that the disturbance to the nerve supply of the stomach is minimal and localized about the stoma This inference was further borne out by the fact that sensation and secretion were intact throughout the stomach It is appreciated, however, that such stomach reflexes that depend on the swallowing of food and its passage down the oesophagus are impaired or missing Because at operation the stomach had been rotated forward, the pylorus was directed posteriorly as shown in Fig 2, and was visualized with extreme difficulty On one occasion, however, the pyloric antrum was satisfactorily viewed with the gastroscope The contractions of the sphincter were not seen The color of the exposed collar of mucous membrane was perhaps slightly redder than that within the stomach, and the external folds were thicker The surface of the mucosa here revealed the same small villi which were seen within, but they appeared slightly flattened and blunted

The color of the mucous membrane within the stomach as well as that exposed on the abdominal wall varied from time to time from a faint yellowish pink to an intense cardinal red The changes in color of the mucosa within the cavity of the stomach were always reflected in the collar of mucosa exposed on the abdominal wall and when changes occurred on the outside they could also be seen within The circumstances with which the changes in color were associated will be discussed in later chapters

The Coating of Secreted Mucus The mucosa within the stomach as well as that exposed on the abdominal wall was

ordinary lighted anoscope, which was inserted into the stoma Thereby it was possible to see nearly the whole mucous membrane of the stomach The examination was facilitated by attaching to the anoscope a transparent balloon,* which could be inflated to separate the stomach walls Without inflation, the anterior and posterior walls were found to be collapsed upon one another The mucosa was pink and thrown up into folds varying in thickness according to the degree of distention of the organ The surface of the stomach mucosa was uniform in appearance and slimy to the touch Closely packed tiny elevations appeared over the entire surface, giving it a granular appearance These elevations were about 1 mm in diameter and visible to the naked eye, but were seen easily only with a magnifying glass Under illumination they appeared as high lights Both Beaumont and Richet recognized them and both believed that they could see the gastric juice welling up from them Beaumont[2] wrote that he could see 'innumerable, minute, lucid points from which distils a pure, limpid, colorless, slightly viscid fluid' We were unable actually to see droplets of secretion appearing from these villi There were no blood vessels, erosions, hemorrhagic spots, or exudates seen within the cavity of the stomach In short, the stomach mucosa answered the usual description of a 'normal' stomach as seen on gastroscopy

A gastroscope was introduced through the stoma and the stomach lining examined by Dr J M Ruffin He reported that the color of the membrane and the size and appearance of the folds were altogether normal Their arrangement, however, was somewhat distorted on the anterior wall, presumably due to the creation of the gastrostomy, and there was a small

* Balloons were generously supplied by the General Electric Co Schenectady N Y

regularly covered by a film of transparent mucus At times when its production appeared especially active, it became thick and opaque over certain areas and occasionally rolled up into small whitish flakes, which lay on the surface of the mucous membrane These precipitated bits of mucus were peeled away with some difficulty and were found to be insoluble in the gastric juice Their digestion was only partially effected after incubation with gastric juice for 24 hours It seems likely that they corresponded to the 'aphthous spots,' which Beaumont described in St Martin's stomach as 'white spots resembling coagulated lymph'

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Plan of Study It was thought desirable to study these functions in more detail with the hope of clarifying the mechanisms

involved in the production of symptoms referable to the stomach and duodenum, and of discovering, if possible, the causes underlying the occurrence there of tissue damage In the next chapter accompanying a short review of facts currently available regarding gastric physiology, we have recorded in detail the methods used for making systematic observations of gastric function

Summary and Conclusions Studies were made upon a subject with a large gastric fistula through which he had fed himself for 47 years His stomach was observed by x-ray and direct inspection Measurements of gastric motility and secretion were recorded

It was established that

1 Feeding through a gastric fistula was no detriment to general health, nor was it necessarily conducive to the development of symptoms referable to the gastrointestinal tract

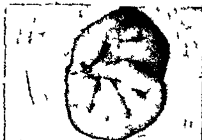
2 The presence of a large opening between the stomach and the outer surface of the body for nearly 50 years did not result in 'gastritis' or in any way vitiate the ability of the stomach to function effectively

3 The motility and secretory functions were found to vary over a wide range under differing conditions The color and general appearance of the mucosa also were found to be variable These changes were compatible with good functioning of the organ

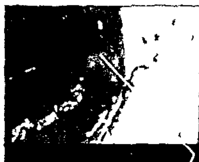
BIBLIOGRAPHY

1 Richet, C Des proprietes chimiques et physiologiques du suc gastrique chez l homme et les animaux, *Jour de l Anat et de la Physiol* 14 170 1878

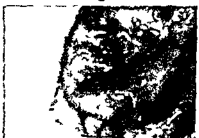
2 Beaumont W *Experiments and observations on the gastric juice and the physiology of digestion* F P Allen Plattsburg 1833 pp 103 and 126











A. Color of the mucosal fold[s] of the normal mucosa during emotional security and relaxation. B. Edematous engorged mucosa with resentment. C. Mucosal erosion associated with hyperactivity, hyperacidity, hypermotility and sustained resentment. D. Matted precipitated mucus after prolonged hyperacidity and [illegible] resentment.

CHAPTER II

The Study of Gastric Function

METHOD OF COLLECTION AND INTERPRETATION OF DATA

THE purpose of the stomach as a digestive organ has been known for centuries The process whereby it receives aliment, mixes it, starts the process of chemical breakdown of proteins and fats, and finally passes it on to the small intestine for further digestion and absorption has been worked out gradually since the publication of Young's thesis in 1803[1] A rapid advance occurred as a result of Beaumont s studies 30 years later and more recently the process has been greatly clarified by studies of a quantitative chemical nature

Briefly, the facts which are currently available are as follows the first mouthful of food as it enters the cardiac orifice of the stomach drops into the hollow of the greater curvature, and subsequently ingested mouthfuls lie on top of it and central to it, forming a sort of stratification The digestive juices reach the outer layers *first* and these are milked along by peristaltic waves peeled off the more central layers as it were, and delivered to the region of the pyloric antrum Here, the acid chyme is partially neutralized by the abundant mucous secretion and the mixture is squirted into the duo-

Circulatory Changes Changes in vascularity were readily recognized by variations in the color of the mucous membrane The latter was easily accessible to view, as pointed out in Chapter I It was seen to undergo a very wide range of

DESIGNATION USED FOR CHARTING		EQUIVALENT IN QUANTITATIVE TERMS (MUNSELL)
100	SCARLET RED	6 25 R 33/10 5
90	↑	6 50 R 35/10 5
80		6 75 R 36/10 5
70		7 00 R 38/10 5
60	COLOR	7 25 R 39/10 5
50		6 00 R 4 2/8
40		6 50 R 4 4/8
30	↓	7 00 R 4 5/8
20	PALE YELLOW RED	8 00 R 5 2/8

FIG 3 Symbols used in expressing color changes in the stomach mucosa The range of color is approximately that of a haemoglobin scale (Talquist type) varying from a pale yellow red to an intense scarlet red

color changes under various circumstances Changes of the same order and in the same direction occurred in the mucosa within the cavity of the stomach as in that part which lay exposed on the abdominal wall Since it was simpler to obtain ideal lighting conditions on the outside, and since there a color scale could be brought up close to the mucosa for comparison, the recorded vascular changes are those observed in the collar of exposed mucous membrane under a cool, 'soft

denum by strong contractile movements The pylorus, which is usually open, closes as the wave of contraction passes over it and thus prevents regurgitation of the food back into the stomach [2]

The gastric juice contains hydrochloric acid, which activates its principal enzyme, pepsin The latter attacks complex proteins and splits them into smaller molecules Some of these are broken down into proteoses and peptones, and even small quantities of amino acids result from peptic digestion in the stomach [2]

Rennin, another important enzyme, coagulates milk It acts on the protein casein, splitting it to yield paracasein and whey albumose Paracasein in the presence of calcium precipitates as a calcium compound [2]

Gastric lipase reduces highly emulsified fats to fatty acids and glycerol [2]

Finally, it is currently held that another substance called 'intrinsic factor' exists in the normal stomach It is said to act on certain ingested foods to form a compound essential for hematopoiesis [4]

Method of the Present Study

A further consideration of the chemistry of digestion is not relevant to the present work Rather our interest is focused on the factors which govern the circulatory, motor, and secretory functions of the stomach

Our subject came to the laboratory in the morning in a fasting state, and reclined for one-half hour on a cot before observations were begun An effort was made to keep the subject's surroundings as neutral as possible and to keep him lightly diverted

ever, the motility pattern is still poorly understood A comprehensive review of the work done on this subject is included in the book by Alvarez[5] He concludes that one type of motility consists of gentle waves of contraction which originate in the cardia and progress towards the pylorus As they do so, the force of contraction increases They may pass over into the pylorus or may end in a 'systolic' contraction of the pyloric antrum A second type of motility pattern is a slow tonic type of contraction in which virtually the whole stomach wall participates, consequently raising the intragastric pressure These recurring waves were found by Cannon[6] to be accompanied by pangs of hunger Hunger has been noted in their absence however, and it has been observed that contractions of other parts of the gut, as well as the stomach, may give rise to pangs of hunger[7]

Recording of Gastric Contractions Records of contractions were obtained by the familiar technic of recording pressure changes in a balloon introduced into the stomach An inlying latex balloon was inflated to a pressure of 10 cm of water and connected to a U tube half filled with water and containing a floating cork with a writing arm The latter recorded the amplitude of gastric contractions in ink on a revolving drum A simultaneous tracing was made with an ordinary pneumograph attached just above the lower margin of the rib cage Thus were recorded respiratory excursions as well as coughs yawns, and body movements These altered the intragastric pressure and caused artefacts' on the record of gastric motility Fig 4 illustrates the way actual stomach contractions can be readily distinguished from artefacts by this method It must be emphasized that the balloon recording-device measures only those contractions which alter the intragastric pressure It has been suggested that certain peristaltic waves may course

white' fluorescent light suitably placed to provide constant lighting conditions The color changes ranged from a faint yellowish red to a deep cardinal shade The standard colors used were evaluated quantitatively by the Munsell method * The quantitative values appear in Fig 3 Opposite them are the numbers, which, for the sake of simplicity, we used in charting the data

Although the cardinal red blush of hyperaemia was easily distinguished from the cyanosis which occurred if the stoma were firmly plugged and the exposed collar of mucous membrane thus isolated from its blood supply, it could not be assumed that the increased redness actually reflected increased blood flow However, *it has been shown by a modification of* the thermal gradient technic, described elsewhere[4] that these color changes do in reality reflect changes in blood flow

Accelerated blood flow in the mucosa was not merely associated with blushing of its surface The membrane itself became wet, swollen, and turgid, and the rugae were slightly fuller and smoother These evidences of vascular engorgement were especially obvious in the collar of mucosa exposed on the abdominal wall During marked hyperaemia, it often doubled in thickness from 5 mm to 10 mm and the radial folds in this exposed collar of gastric mucosa (Fig 1) decreased in number from 12 or 13 to 5 or 7 The tissue itself under such circumstances felt succulent and boggy

Motor Activity in the Stomach The pattern of motility of the stomach, which is provided by the interaction of the circular and longitudinal muscles in its wall, has been observed through fistulae and at operation, and also has been recorded on kymographic tracings and on moving-picture film Because all of these methods of study alter the usual relationships, how-

* *Munsell Book of Color* Munsell Color Co., Baltimore Md.

of three or four separate secretory products and possibly other fluids Therefore, its composition varies within wide limits This difficulty has greatly hindered studies of the nature of gastric juice and the mechanisms governing its production The following facts, however, are well substantiated

The parietal cells are responsible for providing the acid of gastric juice[8] Three other secretory products mucus, pepsin, and rennin and probably other fluids are also present in the mixture Their resultant reaction is alkaline, and they have therefore been grouped together for convenience under the term 'alkaline component'[9]

The parietal cells elaborate at a variable rate a product of constant composition containing little else but hydrochloric acid in a concentration between 16 N and 17 N This is known to be isotonic with the blood[10, 15] The 'alkaline component' is also secreted in concentration isotonic with the blood, and its composition varies within such narrow range that for most practical purposes it may be considered uniform[16] Thus, concentration of acid in gastric juice depends upon the relative amounts of parietal cell secretion and alkaline component' present, and the concentration of the two constituents must bear a linear relationship to one another[12, 15, 17] This was demonstrated experimentally in analyses of random samples of gastric juice for concentration of neutral chlorides, which was taken as an index of the quantity of alkaline component' present and hydrochloric acid Mucus is chiefly if not wholly responsible for neutralizing the product of the parietal cells[17, 19, 20]

The resting stomach continuously secretes gastric juice at a relatively slow rate This juice contains both hydrochloric acid and 'alkaline component'[18] The secretion of acid by the cells of the gastric mucosa is known to be influenced by a

along the stomach without causing a change in intragastric pressure[5]

Collection of Gastric Juice During the experiments in which motor activity was recorded, continuous aspiration of the stomach contents was carried out through a small rubber tube accompanying the balloon Collections made thus, when the walls of the stomach were held apart by the presence of

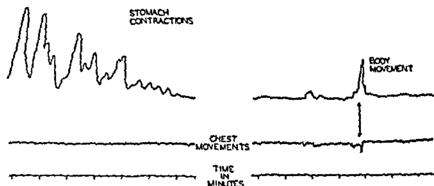


FIG 4 Differentiation of artifacts from actual contractions of the stomach wall by means of a simultaneous pneumographic tracing from the lower margin of the chest.

the balloon, effected satisfactory emptying of the stomach In the absence of the inflated balloon, however, the gastric juice collected in isolated folds of the collapsed stomach and was thus not thoroughly accessible to aspiration through a tube

The completeness of the collection when the balloon was in place was confirmed by removing the balloon after collection of secretion through the tube and rolling the patient over on his left side approximately 120° No additional fluid poured out This latter method of obtaining gastric juice was used at one-half-hour intervals during experiments when motility was not being recorded

Properties of Gastric Juice It is known that gastric juice is not a secretory product of one group of cells but a mixture

of three or four separate secretory products and possibly other fluids Therefore, its composition varies within wide limits This difficulty has greatly hindered studies of the nature of gastric juice and the mechanisms governing its production The following facts, however, are well substantiated

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The resting stomach continuously secretes gastric juice at a relatively slow rate This juice contains both hydrochloric acid and 'alkaline component [18] The secretion of acid by the cells of the gastric mucosa is known to be influenced by a

number of agents[21-28] Furthermore, changes in acid secretion have been correlated with the affective state of the individual[29-31] It should be emphasized, however, that variations in acid production do not necessarily reflect parallel changes in the output of pepsin or mucus.

The available evidence indicates that various stimuli may effect differently the glands of the gastric mucosa. The studies *of Vineberg, for example, suggest that mucoid, chief, and* parietal cells are supplied by separate fibers of the vagus nerve and that each exhibits an individual threshold to electrical stimulation[32] Moreover, histamine appears to exert a selective effect upon gastric secretion, evoking chiefly hydrochloric acid and comparatively little mucus or pepsin[33-35]

Similarly, inhibitors may have a selective influence on the constituents of gastric juice. Although fat appears to inhibit all secretory elements of the gastric glands,[27, 48] an excess of acid in the stomach, as will be shown by evidence adduced later in this study, acts as a powerful stimulus to mucus secretion and an inhibitor to the production of hydrochloric acid (see p 69)

While there is but meager knowledge available regarding the mechanisms involved in the elaboration of hydrochloric acid by the gastric mucosa, we know more of the behavior of the parietal cells than we do of the cells which secrete pepsin and mucus. It has been shown, for example, that the production of acid parietal juice involves an expenditure of energy of approximately 800 calories per liter of secretion[36] To accomplish that work, supplies of oxygen and of carbon dioxide *are required by the cells[37-40] Thomas has recently reviewed the* available literature on the behavior of the various gastric glands[41] In an effort further to clarify their function, the gastric juice of our subject was analyzed as described below under a wide variety of circumstances.

Analysis of Gastric Juice The gross appearance of the specimens was noted The degree, if any, of discoloration with bile was recorded The relative concentration of mucus was estimated by noting the comparative viscosity of the fluid and the presence of shreds Peptic activity was determined by the method of Mett[4] The concentration of acid was estimated by titration of the specimens against 0 1 N sodium hydroxide with Toepfer s solution and phenolphthalein as indicators of 'free' and 'total acidity, respectively

No method was available for the estimation of the output of hydrochloric acid by the parietal cells Since acid is manufactured only by the parietal cells, however, it seemed clear that total hydrochloric acid was some function of volume of juice secreted within a specified time and the concentration of acid Therefore recourse was had to the work already quoted, and parietal cell output was calculated from the relationship which has been established between hydrochloric acid and neutral chlorides[1, 15]

Calculation for Parietal Cell Output Reference to Fig 5 will show that the lower end of the line which relates neutral chlorides to total acid ends near 166 millimoles of hydrochloric acid (total titratable acid of 166) A specimen of gastric juice containing this concentration of acid would consist of pure parietal secretion At the other end of the curve, the constituents of the alkaline component are at a maximum and there is no parietal secretion present At a point half way along the ordinate and abscissa, we are dealing with a solution containing a 50 per cent concentration of each of the constituents Perpendiculars dropped from each of these points intersect at the mid point of the curve Therefore, at suitable intervals along the curve (Fig 5), perpendiculars may be dropped onto

the abscissa to denote what per cent of a solution of certain titratable 'total acid' is actually made up of parietal cell secretion Figures for total acid, of course, correspond numerically to millimoles of hydrochloric acid Multiplying the percentage

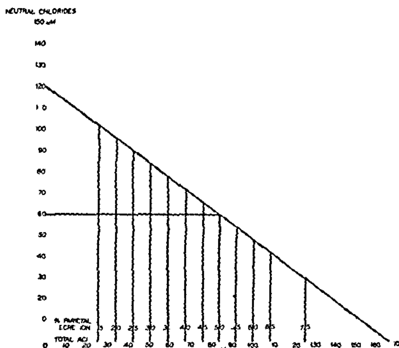


FIG 5 The relationship between parietal cell secretion (HCl) and Alkaline Factor (neutral chlorides) as they occur in gastric juice (Modified from Hollander [11] to show how parietal cell output may be calculated from the total acid value)

figure by the volume of gastric juice secreted within a given time yields the approximate quantity of parietal cell secretion elaborated during that period

Sources of Error in Calculation for Parietal Cell Output The value thus obtained would of course, not be entirely accurate since the graph (Fig 5) was established on the basis of a statistical relationship, and individual specimens must be expected to vary slightly from the mean Furthermore, the

calculations were based on analyses of pure gastric juice in a blind stomach pouch Any admixture of the juice with saliva or bile or any loss of juice through the pylorus would introduce a source of error In this particular case, of course, the gastric juice could not be contaminated by saliva since the oesophagus was completely occluded It is noteworthy that all these sources of error when operating would alter the calculations in the same direction, that is, they would lower the figure for parietal cell secretion obtained Therefore, one is justified in concluding from the calculations that at least that amount of parietal secretion had occurred

Observations on the Sources of Error in Calculation for Parietal Cell Output

1 *Duodenal Contents* Contamination of gastric juice with regurgitated duodenal contents was readily recognized by the presence of bile tint in the specimen Contamination with bile was found to alter greatly values obtained for free acid but total acid readings were little affected even when specimens were heavily tinged with bile as shown in the following observation

After 4 cc of gastric juice had been poured out of the stomach in the usual way, the collecting vessel was changed The next 4 cc, collected in a separate glass, happened to be heavily tinged with bile The specimens were titrated against 0 1 N sodium hydroxide separately for free and total acid with Toepfer's and phenolphthalein as indicators respectively The free acid value in the clear specimen was 64, in the bile-stained specimen, 7 The values for total acid were within 2 points of one another 67 in the clear specimen, and 65 in that which was heavily contaminated with bile

Despite this close correspondence, bile-tinged specimens were not used in attempts at a careful estimate of parietal cell output

2 *Loss of Secretion through Pylorus* Loss of secretion through the pylorus could not be so easily detected as could contamination with bile At times, however, it was possible to recognize that emptying had occurred For example, when one specimen was heavily tinged with bile and the next contained none, it was clear that the gastric content had been flushed through the pylorus, taking with it the residual bile-stained material It was not possible to get a quantitative estimate of the loss, however, under these circumstances Bile almost always appeared in the specimens withdrawn when the previous specimen had contained an unusually high concentration of acid It was as if the duodenal secretions had been regurgitated in order to neutralize excess stomach acidity

With an inlying balloon inflated to a pressure of 10 cm of water and connected to the recording device already described, records of gastric contractions were made Gastric emptying through the pylorus was always observed during periods of active motility Contractions of relatively low amplitude or infrequent contractions resulted in only partial emptying During a period of vigorous motility 30 cc of 0 02 N hydrochloric acid was introduced into the stomach, 15 minutes later only 1 cc of fluid could be recovered It contained 53 clinical units of total acid One-half hour later in an inactive phase when no large contractions were taking place 30 cc of 0 02 N hydrochloric acid was again introduced, 15 minutes later 40 cc of fluid was recovered which yielded 46 units of total acid on titration

During both periods the mucous membrane, whose color throughout was about 70, was actively secreting acid, as could

be inferred from the fact that the very weak solution introduced in each case contained over twice the concentration of hydrogen ions upon withdrawal During the motile phase the fluid introduced and the acid manufactured during the 15-minute period was nearly evacuated through the pylorus while during the quiescent phase the mixture remained in the stomach until it was withdrawn

A pale mucosa always indicated a quiescent stomach No vigorous contractions occurred when the color of the mucosa was 50 or below The effect of introducing 30 cc of 0 02 N hydrochloric acid during pallor and quiescence is shown in Fig 6 The color of the mucosa was 45, and the acid output was low One-half hour after the solution was introduced, 30 cc of fluid was recovered which showed approximately the same concentration of hydrogen ions as the solution which was introduced This indicates that little secretion took place during this period

Comment The significance of these observations is clear In the presence of a pale mucosa no appreciable loss of gastric content occurred, while when the mucosa was red the stomach might or might not empty, depending on whether or not vigorous contractions were occurring

Thus the calculation for parietal cell activity when the mucosa was relatively pale was reasonably accurate On the other hand if with a red mucous membrane vigorous motility occurred the value might be too low It will be shown later that a red mucosa is a constant accompaniment of active parietal cell secretion Therefore, with reference to these constant relationships one may always make a relatively close approximation of parietal cell activity

Summary The methods by which the dynamic functions of the stomach were studied have been reviewed Vascular

changes were observed as color changes in the mucosa That these changes actually reflected alterations in blood flow was shown in a previous study published separately Gastric contractions were recorded directly by means of the balloon

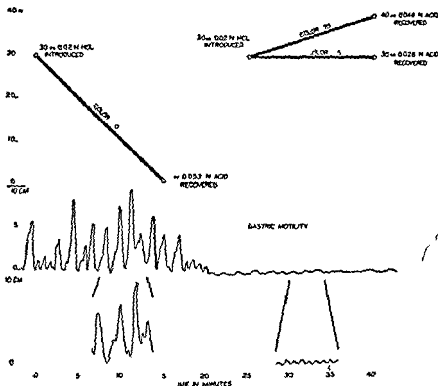


Fig 6 Correlation of gastric emptying with motility On the bottom line appeac actual samples of the motility tracing They are schematized on the line above

technic The estimation of acid secretion, however, was found to be difficult because gastric juice not only contains the secretion of the acid-secreting (parietal) cells, but it is a mixture of several secretory products A method of estimating parietal cell output has been described and its limitations established The principal source of error stems from loss of secretion through the pylorus This loss was shown to occur only in

the presence of vigorous gastric contractions, thus establishing the reliability of the calculation when the stomach was quiescent Even in the presence of vigorous contractions the error could occur only in the direction of making the value obtained too low Therefore, one could conclude that, whatever the figure obtained for parietal cell output under any circumstances, at least that amount of secretion had taken place

Interpretation of Data The experiments cited in the succeeding chapters have been selected to illustrate various phenomena of gastric function In each case several observations were made and the results were confirmed repeatedly before an illustrative example was included in the text.

Conclusions 1 It has been possible to record simultaneous observations on gastric vascularity, motor and secretory activity

2 Changes in vascularity as evidenced by color changes in the stomach lining actually reflected changes in blood flow

3 The stomach emptied only during periods of vigorous contractions

4 The rate of acid production in the stomach was estimated under varying conditions in terms of parietal cell output

5 The principal error in the calculation occurred because of loss of stomach content by emptying through the pylorus

BIBLIOGRAPHY

1 Young J R *An experimental inquiry into the principles of nutrition and the digestive process* Univ of Pa. Medical Thesis, Philadelphia, 1803

2 Cowgill G R The physiology of the alimentary tract,' *MacLeod's Physiology in Modern Medicine*, p 887 9th ed., C. V Mosby St. Louis 1941

3 Castle W B *The etiology of pernicious and related macrocytic anemias* Harvey Soc Lect. Oct. 1934.

4 Richards, C H, Stewart Wolf and H G Wolff 'The measurement and recording of gastroduodenal blood flow in man by means of a thermal gradientometer, *Jour Clin Invest* 21 551, 1942

5 Alvarez, W C *An introduction to gastroenterology*, Hoeber N Y, 1940

6 Cannon W B, and A L Washburn 'An explanation of hunger, *Am J Physiol* 29 441, 1912

7 Patterson, T L, and D J Sandweiss *The simultaneous gastric and duodenal motility phases in man*, Proc Am Physiol. Soc., 1942, p 66

8 Collip, J B *On the formation of hydrochloric acid in the gastric tubules of the vertebrate stomach*, Univ Toronto Studies Physiol, Series No 35, Toronto Univ Library, 1920

9 Hollander, F The composition of pure gastric juice, *Am J Digest Dis* 1 319 1934

10 Pavlov, I *The work of the digestive glands*, English translation from the Russian by W H Thompson C. Griffin & Co, London 1910

11 Hollander, F, and G R Cowgill Studies in gastric secretion. I Gastric juice of constant acidity, *J Biol Chem* 91 151, 1931

12 Hollander F Studies in gastric secretion III Evidence in refutation of the Rosemann theory of hydrochloric acid formation, *Am J Physiol* 98 551, 1931

Hollander, F Studies in gastric secretion. IV Variations in the chlorine content of gastric juice and their significance,' *J Biol Chem* 97 585, 1932

Hollander, F Studies in gastric secretion V The composition of gastric juice as a function of its acidity, *J Biol Chem* 104 33 1934.

13 Bolton, C and G W Goodhart Variations in the acidity of the gastric juice during secretion,' *J Physiol* 73 115 1931

14 Wilhelmj C M I Neigus, and F C Hill Studies on the regulation of gastric acidity I Influence of acid on the secretion of hydrochloric acid by fundic pouches and by the whole stomach, *Am J Physiol* 106 381, 1933

15 Gray J S G R Bucher and H H Harman 'The relationships between total acid and neutral chlorides of gastric juice,' *Am. J Physiol* 132 504, 1941

16 Gray, J S, and G R. Bucher The composition of gastric juice

as a function of the rate of secretion *Am J Physiol* 133 542 1941

17 Helmer O M The relation of the secretion of mucus to the acidity of the gastric juice *Am J Physiol* 110 8 1934

18 Carlson A. J Contributions to the physiology of the stomach 1 23 Beginning in *Am J Physiol* 31 151 1912

19 Bolton C and G W Goodhart The mucus factor in the automatic regulation of the acidity of the gastric contents' *J Physiol* 77 287 1933

20 Grant R Calcium in gastric mucus and regulation of gastric acidity *Am J Physiol* 135 496 1942 (Jan)

21 MacLean H and W J Griffiths The factors influencing the concentration of hydrochloric acid during gastric digestion *J Physiol* 65 63, 1928

MacLean, H and W J Griffiths The automatic regulation of gastric acidity Ibid 66 356 1928

MacLean H W J Griffiths and B W Williams Variations in the acidity and total chloride contained in the secretion from an isolated Pavlov pouch in the dog Ibid 65 77 1928

22 Abbott W O Acetyl B Methylcholin II The action on the gastrointestinal tract of normal persons in abdominal distention and in certain other conditions *Am J Med Sci* 186 323 1933

23 Gray J S and A C. Ivy Effects of mecholyl on gastric secretion *Am J Physiol* 120 705 1937

24 Necheles H W G Motel J Kosse and F Neuwelt The effects of acetylcholine acetyl B methyl choline and prostigmine on the secretion of the stomach of man and dog *Am J Dig Dis* 5 2 4 1938

25 Beaumont W *Experiments and observations on the gastric juice, and the physiology of digestion,* F P Allen Plattsburg 1833

26 Edkins J S The chemical mechanism of gastric secretion, *J Physiol* 34 133 1906

27 Gray J S W B Bradley and A C Ivy On the preparation and biological assay of enterogastrone *Am J Physiol* 118 463 1937

28 Gray J S E Wieczorowski and A C Ivy Inhibition of gastric secretion in man with urogastrone *Am J Dig Dis* 7 513 1940

29 Cade A and A Latarjet Realisation pathologique du petit estomac de Pavlov Etude physiologique et histologique *J de Physiol et de Path Gen* 7 221 1905

30 Cannon, W B 'The influence of emotional states on the functions of the alimentary canal,' *Am J Med Sci* 137 480, 1909
31 Mittelmann B and H G Wolff Emotions and gastroduodenal function Experimental studies on patients with gastritis duodenitis and peptic ulcer,' *Psychosomatic Med* 4 5 1942
32 Vineberg, A M 'The activation of different elements of the gastric secretion by variation of vagal stimulation *Am J Physiol* 96 363, 1931
33 Vineberg A M., and B P Babkin 'Histamine and pilocarpine in relation to the gastric secretion' *Am J Physiol* 97 69 1931
34 Gilman A, and G R Cowgill 'The effect of histamine on the secretion of gastric pepsin' *Am J Physiol* 97 124, 1931
35 Ihre Bengt Human gastric secretion A quantitative study of gastric secretion in normal and pathological conditions, *Acta Med Scand Suppl* No 95 1938
36 *Davenport H W, and R B Fisher* 'The mechanism of the secretion of acid by the gastric mucosa, *Am J Physiol* 131 165 1940
37 Apperly, F L, and M K Cary The relation of gastric acidity to the erythrocyte content of the blood, *Am J Dig Dis* 3 466 1936
38 Alvarez, W C and F R Vanzant The relations between hemoglobin and gastric acidity,' *Proc Staff Meet of Mayo Clinic,* 11 385, 1936
39 Pickett, A D., and E. J Van Liere 'The effect of anoxia on gastric secretion from Pavlov and Heidenhain pouch dogs, *Am J Physiol* 127 637, 1939
40 Van Liere, E J and P E. Vaughan 'Basal secretion of Pavlov pouch dogs as influenced by oxygen want,' *Am J Dig Dis* 8 155 1941
41 Thomas J E The modern conception of gastric secretion,' *J A M A* 120 735, 1942
42 Hawk P B., and O Bergeim *Practical physiological chemistry,* P Blakiston s Sons and Co Inc, Philadelphia 1937 Ed 11, p 308 (Method of Mett)
43 Shay H J Gershon Cohen and S S Fels 'The role of the upper small intestine in the control of gastric secretion *Ann Int Med* 13 294 1939

CHAPTER III

Correlation of Motor Activity, Secretion, and Blood Flow

FACTORS WHICH PRIMARILY AFFECT MOTOR ACTIVITY

1 *Inhibition of Contractions by the Introduction of Fluids Directly into the Stomach.* Liquids of various sorts were introduced rapidly into the stomach through a tube in amounts of 30 cc. In each case there occurred a temporary inhibition of gastric contractions if such were present. The duration of the inhibitory effect varied with the composition of the fluid. Physiological saline solution or gastric juice at body temperature had only a very slight effect. If either was warmed or cooled before introduction its effect was more prolonged, inhibiting 2 or 3 waves. Tap water at body temperature similarly inhibited contractions very briefly. Alkalies were tested in concentration ranging between 0.02 to 0.05 N sodium *hydroxide*. The duration of the inhibitory effect was proportional to the concentration of alkali. Maximum inhibition was for 15 minutes. Acids ranging from 0.02 to 0.33 N hydrochloric acid were similarly tested and also found to exert an inhibitory effect upon contractions proportional to their

strength 0 33 N hydrochloric acid arrested gastric contractions for 30 minutes Usually when the stomach contractions started up again, the first waves were as high as, or slightly

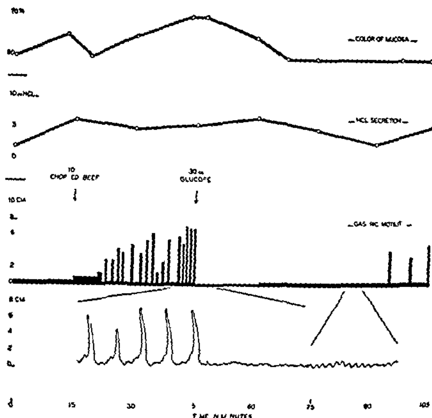


FIG 7 Inhibition of gastric motility by the introduction of glucose solution through the stoma On the bottom line appear actual records of motility These are represented diagrammatically on the line above

higher than, the last waves before the period of inhibition Occasionally, however, there occurred 3 to 5 preliminary waves of low amplitude before the original pattern was re-established All types of fluids including foods were found to have a temporary inhibitory effect upon gastric contractions Fig 7 shows the typical pattern of temporary inhibition of

motility by 30 cc of 50 per cent glucose poured in through the stoma during a phase of vigorous contractions Commonly 1 or 2 additional gastric contractions occurred following the introduction of fluids before inhibition was effected

Introducing less than 30 cc of fluid failed to inhibit gastric contractions except in the case of 0 33 N hydrochloric acid 15 cc of acid in this concentration inhibited them for nearly as long as 30 cc of 0 1 N hydrochloric acid

It was not feasible to test the effect of introducing more than 30 cc of fluid, since a proportion of larger amounts escaped through the stoma after introduction

The inhibitory effect of these solutions varied not only with respect to their compositions and the quantities introduced, but also according to the phase of motility during which they were introduced Soon after the vigorous contractions started, the inhibition was effected most readily Introduced 15 minutes later however, the same solution inhibited contractions for shorter time Introduced during the period of incomplete tetanus near the end of the phase of motility, the weaker inhibitors produced no effect at all, and the stronger ones only the most fleeting inhibition of 1 or 2 waves

Effect of Sudden Distention of the Stomach and Mechanical Irritation During a phase of vigorous contractions, 10 20 and 50 cc of air were suddenly introduced into the inlying balloon Aside from raising the base line, no effect on the stomach contractions was noted

Similarly stimulation of the stomach lining with a glass rod during such a phase failed to inhibit contractions

Effect of Ingestion of Food 100 gms of dry cooked chopped beef introduced into the stomach during a period of vigorous contraction failed to alter the pattern of the waves within 10 minutes

Similarly, 50 gms of boiled potato and 20 gms of bread were tried without detectable effect

10 cc of viscous mayonnaise was introduced into the cardiac end of the stomach while a duodenal drainage tube was in place in the duodenum Gastric contractions continued for 5 minutes and then stopped abruptly as the fat globules first appeared in the material aspirated from the duodenum

Effect of the Introduction of Fluids Directly into the Duodenum The introduction of distilled water, weak acid solutions, and other fluids directly into the duodenum through a tube resulted in more prompt inhibition of gastric contractions than was observed when the material was placed in the stomach The duration of the effect was approximately the same

Comment Much interest has been manifested by workers in the past [1,3] in the inhibition of 'hunger' contractions by the introduction of fluids into the stomach Carlson [1] observed the effect not only after introducing almost any fluid into the stomach, but after chewing movements, during vigorous exercise, exposure to intense cold and accompanying a reaction of fear The mechanism which underlies the phenomenon has not been adequately explained The inhibition by fluid is certainly not due to its mechanical contact with the mucosa of the stomach, since the introduction of solid pieces of meat, or mechanical stimulation with a glass rod, does not effect an inhibition of contractions Neither does separation of the stomach walls, by increasing the stomach content, offer an adequate explanation, since the sudden increase in size of the inlying balloon, by the introduction of additional air, did not inhibit contractions

The fact that one or two additional gastric contractions usually occur following introduction of the fluid into the

stomach before inhibition is effective suggests that the reflex inhibition arises in reality from the duodenum This notion gains support from the experiment related above, when fat was introduced into the cardiac end of the stomach Inhibition of gastric contractions did not occur until the fat had reached the duodenum Furthermore, as already noted, when fluids were introduced directly through a tube into the duodenum no additional gastric contractions occurred Inhibition was immediate

Whatever its mechanism the inhibitory effect of the introduction of fluids on gastric contractions is believed by many to be responsible for the relief from the pain of peptic ulcer which follows the ingestion of alkalies or milk Christensen [4] has shown a striking correlation between pain and hunger contractions in patients suffering from peptic ulcer The relief of pain following the ingestion of milk or alkalies corresponded with the period of inhibition of vigorous contractions

This may provide an adequate explanation of the relief of pain, unless some other pain-inducing factor is present For example we found that strong acid introduced into the stomach effectively inhibited contractions yet Palmer [5] has shown and indeed it has been the experience of others, that the ingestion of acid actually accentuates the pain of ulcer

Furthermore in the presence of ulcer or even inflammation of the mucous membrane, this inhibitory action of fluids may be lost Shay and his collaborators have found that patients with peptic ulcer and duodenitis do not exhibit a cessation of vigorous gastric contractions or decrease in output of acid which is also known to occur normally when fluids are introduced into the duodenum [6] We have made a similar observation, finding acceleration in the output of gastric acid in the

presence of erosions of the gastric mucosa The data are discussed in Chapter IX

Effect of Swallowing Despite the fact that our subject s oesophagus was completely occluded, swallowing small amounts of water into the blind oesophageal sac or even making swallowing movements with the mouth empty caused momentary inhibition of a gastric contraction if one was occurring at the time

Like other inhibitory influences, swallowing became less effective near the end of the phase of vigorous contractions and failed altogether to influence the terminal period of incomplete tetanus

2 *Stimulation of Contractions by a Sudden Distention of the Stomach* On ten occasions during a phase of quiescence, when the balloon was inflated to a pressure of 10 cm of water, additional air was suddenly introduced, which doubled the intragastric pressure Eight times out of the ten, no contractions were induced by this method On the other two occasions, two isolated vigorous contractions occurred before the stomach became quiescent again Rapid alternating increases in pressure, continued for 30 seconds, were not more effective in inducing motility

Simultaneous Observations of Vascularity, Motor Activity, and Secretion

Basal Levels of Blood Flow, Motility, and Secretion During periods when the subject was well relaxed and apparently secure emotionally, the color of the mucosa remained relatively constant at approximately 50 Contractions were usually of low amplitude and rhythmic, making a pattern of three small waves a minute One such pattern is illustrated in Fig 8

Gastric juice accumulated in the stomach at the rate of approximately 8-15 cc an hour Total acid under these circumstances averaged 50 clinical units In terms of parietal cell output as calculated by the method already described, this represents about 5 cc an hour when specimens were withdrawn at 30-minute intervals When the fluid was allowed to

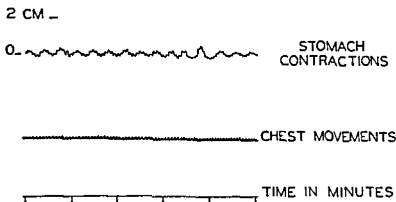


Fig 8 Sample of gastric contractions during basal period

run out of the stomach continuously, the rate of parietal cell output was slightly higher, 7½ cc an hour Allowing the fluid to accumulate within the stomach and withdrawing it only at the end of 3 hours slowed the rate of parietal secretion to 3 cc an hour This secretion persisted whether or not a balloon or stomach tube was introduced into the stomach With the stomach empty and untouched and the subject sleeping, acid fluid was seen to accumulate at the same rate as measured when the balloon was in place Because of the absence of vigorous contractions at this time, loss of secretion through the pylorus need not be considered

Comment It seems likely that the regularly recurring rhythmic waves of contraction, which alter very little the

intragastric pressure, represent the effect of continuous peristaltic activity Thus they would correspond to Alvarez' first type of motility[7]

As motor activity is continuous during 'basal' conditions, so we found acid secretion to be continuous Its rate of secretion was slightly accelerated by withdrawing the stomach content This finding suggests that the presence of acid in the stomach inhibits to a degree further secretion This possibility will be explored later Carlson[1] too found in his subject that a relatively slow rate of secretion was always present during rest and even sleep Beaumont[8] stated that each morning he found Alexis St Martin's stomach empty, but that after introducing a rubber tube he was able to obtain secretion promptly He inferred from this that the mechanical irritation of the tube had caused the gastric juice to be secreted Actually the presence of a tube does not stimulate secretion, as pointed out above The tube simply enabled him to gain access to the juice which was hidden in the folds of St Martin's collapsed stomach Therefore, it seems likely that St Martin too had a continuous basal rate of secretion in his stomach It is probable, however, that acid secretion stops altogether in some individuals during basal conditions, since in many presumably healthy people gastric analysis yields no titratable acid in the absence of an applied stimulus

In this connection, recent work done by Gordon and Chernya in Russia is of interest[9] In 3 patients with artificial gastrostomies who had basal free acid values ranging from 12 to 40 clinical units, a pronounced decrease in volume of secretion and a disappearance of 'free acid was effected by hypnotic suggestion during which the patients were led to believe that they were 'at complete rest and free of emotional conflict'

Spontaneous Periodic Phases of Accelerated Gastric Function

Gastric Contractions Approximately every 2-3 hours there occurred in the stomach a transitory phase of accelerated motor activity which lasted 10-30 minutes Carlson[1] first described these recurring cycles of vigorous contractions He referred to them as 'hunger contractions' This restricted designation appears to be misleading, since we did not find the sensation of hunger associated with these phases more than 50 per cent of the time Individual pangs of hunger could rarely be correlated with the peaks of waves unless the contraction was forceful enough to raise the intragastric pressure to 30 mm of Hg or more (see Chapter VIII) Contractions of such force occurred relatively rarely Often, too sensations of hunger associated with actual cramping abdominal pains occurred in the absence of vigorous contractions

The phases of recurrent motor activity occurred in such a way as to create a characteristic pattern The low 'basal' waves already described and seen to occur at the rate of three a minute, gradually increased in height and duration, finally giving way to a wave of different appearance, which rose quickly to a peak, often with a step-like interval on the way up and fell to the base line even more quickly after the peak had been passed These waves lasted from 10 40 seconds They occurred once every 1-2 minutes at first but gradually became more frequent as they became taller, until finally there was incomplete relaxation between contractions and a state of poorly sustained tetanus developed This usually lasted 1-2 minutes and then the stomach wall suddenly relaxed Following this there occurred a period of apparent total absence of

intragastric pressure, represent the effect of continuous peristaltic activity Thus they would correspond to Alvarez' first type of motility[7]

As motor activity is continuous during 'basal' conditions, so we found acid secretion to be continuous Its rate of secretion was slightly accelerated by withdrawing the stomach content This finding suggests that the presence of acid in the stomach inhibits to a degree further secretion This possibility will be explored later Carlson[1] too found in his subject that a relatively slow rate of secretion was always present during rest and even sleep Beaumont[8] stated that each morning he found Alexis St Martin's stomach empty, but that after introducing a rubber tube he was able to obtain secretion promptly He inferred from this that the mechanical irritation of the tube had caused the gastric juice to be secreted Actually the presence of a tube does not stimulate secretion, as pointed out above The tube simply enabled him to gain access to the juice which was hidden in the folds of St Martin's collapsed stomach Therefore, it seems likely that St Martin too had a continuous basal rate of secretion in his stomach It is probable, however, that acid secretion stops altogether in some individuals during basal conditions, since in many presumably healthy people gastric analysis yields no titratable acid in the absence of an applied stimulus

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coexisting motility precluded satisfactory measurement of parietal cell output during these periods, but the titratable total acid values were found to be significantly elevated, and this indicates that parietal cell activity was accelerated[10]

Comment The occurrence of these spontaneous periodic phases of accelerated gastric function was carefully taken into account, when vascular changes and changes in secretion and motility were attributed to the influence of stimuli applied experimentally Usually such stimuli were applied shortly after the termination of one of these phases when another would not be expected for an hour and a half In addition, the experiments were repeated sufficiently often to establish the validity of the inferences

Effect of Histamine on Blood Flow, Acid Secretion and Motor Activity During a half-hour control period the gastric juice was collected and the color of the mucosa was observed In addition the thermal gradientometer referred to previously[11] was in place inside the stomach to measure changes in blood flow, so that they might be correlated with the vascular changes observed by comparison of the mucosa with the color standard It was not convenient to make the usual record of contractions in addition, but the larger ones could be recognized by the way they milked the tube of the blood flow recorder

After the establishment of a base line 0 0005 gm of histamine phosphate was injected hypodermically The findings are detailed at this point in order to illustrate the vascular changes which accompany accelerated secretion of acid

The results are charted in Fig 10 Within 5-10 minutes of the injection the red color of the mucosa became deeper and there was a parallel increase in recorded blood flow At the same time acid output increased in terms of parietal cell secre-

contractions lasting for 5-10 minutes and being followed then by a resumption of the contractile waves of low amplitude, which recurred at the rate of 3 a minute

Fig 9 shows the pattern of contractions in one of these phases of periodic accelerated gastric contractions The typ-

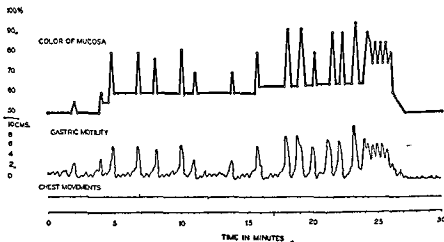


Fig 9 Typical pattern of a phase of accelerated gastric motility with characteristic ending in a period of incomplete tetanus Note changes in color of the mucosa associated with vigorous contractions

ical ending with tetanic contractions, and the ensuing period of quiescence also appears on the chart

Blood Flow The 'basal' waves of low amplitude were not found to be accompanied by any detectable change in the color of the mucous membrane of the stomach The more vigorous contractions, however, were associated with a simultaneous transitory blushing of the mucosa proportional in degree to the force of the contraction Fig 9 shows the correlation of color changes in the mucosa with vigorous contractions of the stomach wall

Secretion The secretory rate of the parietal cells also shared in these periodic phases of accelerated gastric function The

coexisting motility precluded satisfactory measurement of parietal cell output during these periods, but the titratable total acid values were found to be significantly elevated, and this indicates that parietal cell activity was accelerated [10]

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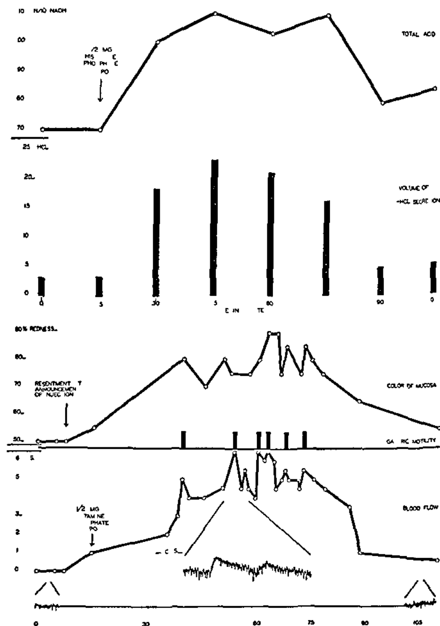


Fig 10 Correlation of gastric functions including recorded blood flow following histamine injection On the lowest line appear samples of the actual record of blood flow which is represented schematically on the line above

tion and total titratable acid It can readily be seen in the graph that the parietal cell output parallels the vascular changes The total acid rises with the others but remains at relatively high levels after the activity of the parietal cells has fallen off (This is presumably because the accumulated mucus was washed out of the stomach during the period of heightened secretory activity and its rate of secretion after histamine was so slow that the product of the parietal cells no matter how small in amount was not neutralized)

Within 25 minutes after histamine injection strong contractions of the stomach wall occurred With each of these there was a transitory blushing of the mucosa and an increase in recorded blood flow

The maximum effect from histamine in terms of secretion, blood flow, and motility occurred in about 45 minutes After 90 minutes the effects had nearly subsided and the values had returned to normal by 2 hours

Comment These data illustrate (1) That vascular changes observed as variations in color of the exposed gastric mucous membrane actually reflect changes in blood flow (2) That histamine stimulated an increase in blood flow and motility as well as in acid production (3) The importance of expressing acid output in terms of parietal cell secretion since the total acid concentration failed to fall to control levels following a phase of accelerated secretion when acid output had subsided

Effects of Alcohol After establishing a base line of vascularity, secretion, and motor activity 30 cc of 90 proof whiskey (45 per cent alcohol by volume) was introduced into the stoma As in the case of histamine an acceleration of all three functions occurred The maximum effect was observed in about 45 minutes, and in approximately 90 minutes the values

had returned to normal A typical experiment is illustrated graphically in Fig 11

Comment Other workers [12, 13] have shown that alcohol need not be introduced directly into the stomach in order to stimu-

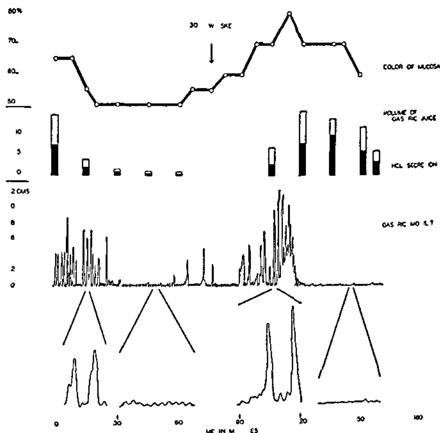


FIG 11 Effect of alcohol on gastric function Whiskey was administered following a period of spontaneous accelerated gastric function Normally a second such period would not follow for at least 2 hours

late the parietal cells to accelerated activity Given intravenously or rectally the drug causes a sharply increased output of acid Our observations indicate that even when ingested, the effects are not the result of local stimulation Hyperaemia

of the mucosa and accelerated secretion did not occur until the drug had had time to become absorbed

Effects of Beef Juice Similar observations were recorded when a beef bouillon cube was introduced into the stoma

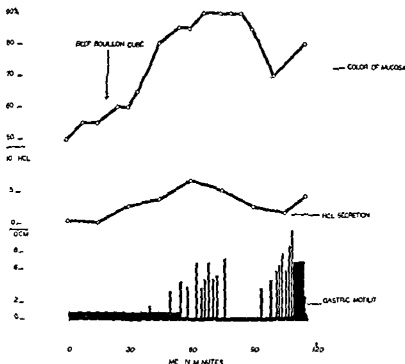


Fig 12 Effect of beef bouillon on gastric function.

Within 15 minutes there occurred a flushing of the mucosa with enhanced secretory and motor activity which lasted more than an hour The results appear in Fig 12

Preparation for Eating Another circumstance known to be associated with accelerated acid output is the feeling of good appetite which accompanies the sight or mere thought of delectable food This has been shown also to be associated with

hyperaemia and hypermotility as illustrated in Fig 13 The vascular engorgement, accelerated acid production, and increased motor activity occurred promptly following the mention of appetizing food Actual presentation and tasting of the food added little to this effect

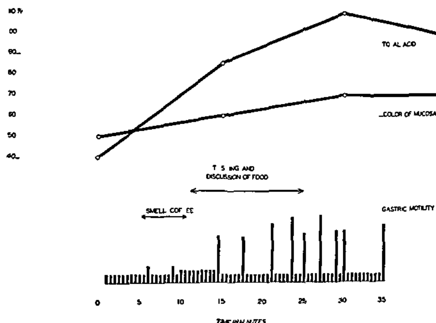


Fig 13 Gastric function associated with stimulation of appetite

Hunger Although, as already mentioned, hunger pains were reported by the subject at times in the absence of stomach contractions, as a rule they were found to be accompanied by vigorous contractions and a relatively red, actively secreting mucosa

Correlation of Blood Flow, Acid Production and Motor Activity—General Statement While profound changes in blood flow, acid production, and motor activity have been observed accompanying various emotional states and other

circumstances, never in this subject were changes in vascularity and acid secretion dissociated. An increase in one was found under all circumstances to be associated with an increase in the other. Conversely, low acid output and pallor of the mucosa have been regularly associated. Vigorous motility has never been observed when the color of the mucosa was 50 or below. In the presence of a red mucosa, vigorous contractions might or might not occur. No correlation was observed between the degree of hyperaemia and the height or frequency of contractions, but accompanying each one was noted a transitory increase in redness of the mucosa, which subsided with the relaxation of the stomach wall.

Discussion. From the observations recorded above it appears to be established that hyperfunction of the stomach, either motor or secretory, is always accompanied by hyperaemia. This leads to the inference that hyperaemia is essential to the acceleration of gastric function. Indeed, it is a general biological experience that heightened cellular metabolism requires increased blood flow. Clearly the blood must carry added oxygen for the muscular work of vigorous contractions and, as noted already on p. 26, secretion of acid by the stomach also requires the expenditure of energy.[14] Experimental confirmation is found in the work of several workers[7, 15, 16, 17] who have found in animals and humans low values for gastric acidity during states of anoxaemia induced by high altitude, low oxygen tension chambers, severe hemorrhage and even polycythaemia. Correction of the anoxic state resulted in a return of acidity values to normal.

A few investigators[18, 19] have recorded combined measurements of blood flow and gastric secretion in animals. Lim, Necheles, and Ni[18] studied gastric blood flow in the excised dog's stomach, perfusing it with another dog's blood. They

demonstrated acid secretion following histamine injections The blood flow, as measured by cannulating the veins, failed to parallel the rate of secretion

Dodds and his co-workers[19] made similar studies on dogs after surgical intervention Instead of resecting the stomach, they left it in place and resected the entire small and large intestine Following this, appropriate vessels to the stomach were cannulated, and the blood flow was measured by collecting the venous blood in a graduated container for a certain length of time The blood was then transfused back into the animal Their findings differed widely from those of Lim *et al* An increase in blood flow was noted with an increase of volume of gastric juice secreted in response to histamine injection They were able to inhibit the histamine effect with regard to volume of gastric secretion and blood flow by giving injections of 'pitressin' * or barium chloride, or by causing a vasoconstriction in the stomach by irrigating it with cold water The titratable acidity, however, remained high

In the interpretation of all of these animal experiments, one must reckon with the trauma of surgical operation, the effects of anesthesia, and the pathological changes induced by the operative procedure

A few observations have been made on circulatory changes in the gastrointestinal tract by direct inspection of the serosal and mucosal coats Kuntz and Haselwood[20] found that a reflex vasoconstriction in the serosal coat of the intestine of the cat was induced by packing ice on the abdominal wall Warming the abdomen was found to cause a vasodilatation in the area

Beaumont[4] recognized in Alexis St Martin that the stomach lining was redder at some times than at others 'On the appli-

* 'Pitressin a brand of beta hypophamine of posterior lobe of pituitary gland Parke Davis Detroit, Mich.

cation of aliment,' he wrote, 'the action of the vessels is increased, the color brightened ' Anger and fear, he noted, produced a 'morbid appearance of the mucosa, although it is not entirely clear from his notes whether under those conditions the stomach was redder or paler Carlson[1] observed in his Mr V a deepening of the red color of the mucosa with each strong contraction of the stomach wall Schindler[21] has described the appearance of the stomach mucosa of patients with peptic ulcers as appearing redder than 'normal through the gastroscope This instrument has not been left in place long enough to follow changes in color for more than a few minutes at a time

Drury, Florey and Florey[22] studied vasomotor changes in a patch of exteriorized colon in dogs They found with alarm or fright a uniform blanching of the mucosa, due presumably to constriction in the large branches of the mesenteric arteries Also, they noted in response to local trauma, and occasionally occurring spontaneously, fluctuating areas of pallor due presumably to the squeezing of blood out of the capillaries by contraction of the muscularis mucosae Barcroft and Florey[23] using similar preparations found pallor marked during brief spurts of running but less marked during prolonged exercise They also found pallor in association with anxiety or excitement

Our studies support these findings—that profound vascular changes occur in the gastric mucosa and in addition that hyperaemia occurs in association with accelerated acid secretion and motor activity, and pallor with a decrease in these functions

Summary The introduction of fluids into the stomach or duodenum effected an inhibition of gastric contractions The duration of the inhibitory effect varied with the time of intro-

duction, the quantity and nature of the fluid Simultaneous observations of motor activity, vascularity, and secretion in the stomach have been recorded During the resting state, the stomach was found to be relatively pale and contracting with rhythmic waves of slow amplitude Acid was secreted continuously in small amounts Merely withdrawing the gastric juice provided a slight stimulus to secretion From time to time there occurred spontaneous phases of hyperaemia, hypermotility, and hypersecretion

The effects of histamine and other stimuli on the various gastric functions were recorded A direct association between vascularity (blood flow) and acid production was found to obtain under all circumstances of accelerated or depressed activity Vigorous contractions, while they did not invariably accompany redness of the mucosa, never occurred in the presence of pallor

Conclusions 1 Inhibition of *gastric* contractions resulted from the introduction of fluids into the stomach or duodenum. The effect was probably due to their contact with the mucosa of the latter

2 The rate of acid production in the stomach was estimated under a variety of conditions with reference to volume of secretion and concentration of acid The results were expressed in terms of parietal cell output (cc of 0 166 N hydrochloric acid)

3 Increased parietal cell output was always accompanied by *hyperaemia of the gastric mucosa Hyperaemia also accompanied* increased motor activity

4 The fasting stomach of this individual secreted acid gastric juice at a relatively constant rate without the application of external stimuli either chemical or mechanical Merely

withdrawing the juice at intervals constituted a slight stimulus to acid secretion

5 On the basis of data gathered from these studies, certain generalizations are possible with regard to the interpretation of the findings on routine gastric analyses performed on patients

a When an unusually large volume of gastric juice of high titratable acidity accumulates in an unobstructed stomach during a specified interval, it is safe to assume that the mucous membrane is relatively red and that no vigorous contractions are taking place in the stomach

b When a small volume of gastric juice of very high titratable acid is obtained under similar circumstances it is likely that the mucous membrane is relatively engorged with blood and that, in addition, especially vigorous contractions are taking place

c Low acid values in the presence of small volumes of gastric juice strongly suggest that the gastric mucosa is relatively pale and that no vigorous contractions are taking place

BIBLIOGRAPHY

1 Carlson A J Contributions to the physiology of the stomach 1 23 Beginning in *Am J Physiol* 31 151 1912

2 Ginsburg H and I Tumpowsky Contributions to the physiology of the stomach 50 Studies on the control of hunger by drugs, *Arch Int Med* 22 553 1918

3 Quigley J P., and K. R Phelps The mechanism of gastric inhibition following the ingestion of carbohydrate' *Amer J Physiol* 109 85 1934

4. Christensen O Pathophysiology of hunger pains, *Acta Med Scand Suppl* No 37 1931

5 Palmer W L Mechanism of pain in gastric and in duodenal ulcer' *Arch Int Med* 39 109 Jan. 1927

6 Shay H J Gershon Cohen, and S S Fels A self regulatory duodenal mechanism for gastric acid control and an explana

tion for the pathologic gastric physiology in uncomplicated duodenal ulcer, *Am J Dig Dis* 9 124 1942

7 Alvarez, W C *An introduction to gastroenterology*, Hoeber, N Y, 1940

8 Beaumont, W *Experiments and observations on the gastric juice and the physiology of digestion*, F P Allen, Plattsburg, 1833

9 Gordon, O L and Y M Chernya Physiology of gastric secretion in man studies on patients with gastric fistula and artificial oesophagus' *Klin Med* (No 12) 18 63 1940

10 Gray J S and G R Bucher The composition of gastric juice as a function of the rate of secretion' *Am J Physiol* 133 542, 1941

11 Richards C H Stewart Wolf, and H G Wolff The measurement and recording of gastroduodenal blood flow in man by means of a thermal gradientometer' *Jour Clin Invest* 21 551 1942

12 Newman, H W., and H G Mehrtens Effect of intravenous injection of ethyl alcohol on gastric secretion in man' *Proc Soc Exper Biol & Med* 30 145 1932

13 Frouin A and M Molinier L action d alcool sur la secretion gastrique,' *Compte Rend Acad de Science* 132 1001 1901

14 Davenport H W and R B Fisher The mechanism of the secretion of acid by the gastric mucosa, *Am J Physiol* 131 165 1940

15 Apperly F L and M K. Cary The relation of gastric acidity to the erythrocyte content of the blood *Am J Dig Dis & Nutr* 3 466 1936

16 Pickett, A D, and E J Van Liere The effect of anoxia on gastric secretion from Pavlov and Heidenhain pouch dogs *Am J Physiol* 127 637 1939

17 Van Liere E. J and P E. Vaughan Basal secretion of Pavlov pouch dogs as influenced by oxygen want, *Am J Digest Dis* 8 155 1941

18 Lim, R K S H Necheles and T G Ni The vasomotor reactions of the (viviperfused) stomach *Chinese J Physiol* 1 381 1927

19 Cutting W C E C Dodds R L Noble and P C Williams Pituitary control of alimentary blood flow and secretion The effect of posterior pituitary extract on the alimentary secretions

of intact animals *Proc Roy Soc* London Series B 123 27 1937

20 Kuntz, A and L A Haselwood Cutaneo visceral vasomotor reflexes in the cat, *Proc Soc Exp Biol and Med* 43 517 1940

21 Schindler R *Gastroscopy the endoscopic study of gastric pathology*, Univ of Chicago Press Chicago 1937 pp 149-57

22 Drury A N H Florey and M E Florey The vascular reactions of the colonic mucosa of the dog to fright, *J Physiol* 68 173 1929

23 Barcroft, J and H Florey The effects of exercise on the vascular conditions in the spleen and the colon *J Physiol* 68 181, 1929

The Influence of Common Physical and Chemical Agents on Gastric Function

1 *Environmental Temperature—Cold* After establishing a suitable base line of gastric function, the windows of the laboratory were opened The temperature outdoors was 0° C The room temperature was lowered to 10° C from 24° C The patient was lightly clad and his abdomen was exposed Within 3 minutes he began to shiver, and his gastric mucosa paled from a control level of 55 to 35 It remained so throughout the period of exposure to cold, which lasted 15 minutes The parietal cell output also decreased perceptibly The windows were then closed and the heat was turned on in the room The temperature quickly rose again and as it did, the patient became warmer and his gastric mucosa blushed to a point redder than it had been before Accelerated acid production and vigorous contractions ensued The events are shown diagrammatically in Fig 14

Throughout the cold days of fall and winter, the gastric mucosa, which was observed 15 minutes to a half hour after the patient had come in out of the cold each morning and had been resting in the warm laboratory, was significantly redder

and more active from the standpoint of acid secretion than during a similar period in summer

Comment It is a common observation that desire for food is enhanced following exposure to cold This may be related

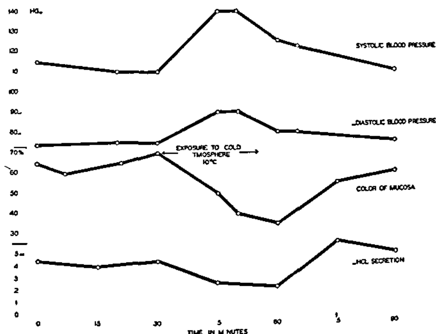


Fig 14 Blood pressure vascular and acid secretion changes in the stomach during exposure to cold

to the accelerated gastric function which, as noted above, occurred at this time

2 *Ice Applied Locally* The application of ice bags locally to the abdominal wall around the stoma had an effect similar to, but less marked than that of a cold atmosphere Results are represented graphically in Fig 15

3 *Irrigation of the Stomach with Cold and Hot Water—Effect on Motor Activity* It has already been pointed out that the introduction of any fluid into the stomach inhibits stomach

contractions temporarily Cold water (9° C) had a longer inhibitory effect than did hot (46° C) water This effect could be demonstrated only when the water was actually introduced into the organ and did not occur when the fluid was irrigated through an inlying balloon

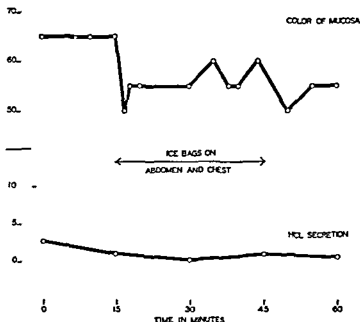


FIG. 15 Vascular and acid-secretion changes in the stomach during local cooling

Effect on Vascularity Irrigation of the stomach with water at 47° C for 15 minutes brought about a slight transitory increase *in redness of the mucosa of not more than 10 points on* the scale which subsided within 2 or 3 minutes of the time of withdrawal of the stimulus

Cold water (9° C) similarly applied to the gastric mucosa effected a blanching of the mucosa of about 10 points, which lasted the same length of time as did the blushing following irrigation with hot water

Effect on Output of Acid In order to test the effects of local application of heat and cold on the production of acid by the gastric mucosa, a balloon was introduced into the stomach, and the hot and cold water were allowed to circulate in and out of this after the manner depicted in Fig 39 (See page 144)

Irrigation with water at 9° C did not influence the production of acid, but during the period of slight hyperaemia following the removal of the cold stimulus there occurred a slight acceleration of acid output

A similar slight acceleration of parietal cell activity occurred during the transient hyperaemia which accompanied irrigation of the stomach with water at 47° C

4 *Tobacco Smoking* Smoking a pipe or cigarettes was not accompanied by any alteration in the pattern of gastric contractions in our subject when the smoking was a pleasurable experience When he had no taste for it, however, and the smoking induced slight nausea, the recorded waves of contraction stopped very promptly and remained absent until the smoking had been discontinued and there were no residual feelings of nausea At this point contractions of the same magnitude as those which had been interrupted started in again

Similarly, vascularity in the stomach and output of acid were unaffected by smoking unless there was an accompanying nausea Under such circumstances a moderate pallor of the mucosa occurred and, with it, an associated decrease in parietal cell activity With the subsidence of the nausea, these values returned to their former levels

Comment These gastric changes, which were found to accompany nausea associated with smoking, led us to explore gastric function during nausea induced by other stimuli

5 *Vestibular Stimulation and Other Measures Which In-*

duce Nausea On 12 occasions, for periods of time varying from 5 to 15 minutes, one external auditory canal was irrigated with cold water between 0° and 10° C On each occasion, whether or not the strength of stimulus was adequate to induce nausea there occurred within one minute of the beginning of irrigation and often before the onset of nystagmus a sharp decrease in the amplitude of gastric contractions This effect lasted throughout the period of stimulation It was followed by a gradual return of the gastric contractions to their former amplitude This return was complete within 10 minutes unless nausea accompanied the stimulus Following nausea, however, the resumption of contractions was delayed for variable periods from 15 to 90 minutes, the length of delay corresponding roughly to the intensity and duration of nausea

Inhibition of gastric contractions and a moderate decrease in redness of the mucosa were the only changes observed in the stomach following a caloric vestibular stimulation which failed to induce nausea When nausea resulted, however in addition to the changes in motor activity there occurred profound pallor of the gastric mucosa and a marked decrease in parietal cell output The volumes of gastric juice obtained at each collection, however, were not reduced owing to a corresponding acceleration of mucus secretion The specimens were noted to be viscid, and titratable acid was low Salivary flow, which was measured by emptying at 15-minute intervals the blind upper end of the subject s oesophagus was much increased during nausea

Nausea induced by various other methods, and that which occurred in our subject spontaneously following dietary indiscretion was also uniformly accompanied by mucosal pallor hypomotility, and hypoacidity in the stomach

It is noteworthy that emotional states involving a reaction of fear and withdrawal were found to be accompanied by pallor and hypofunction of the stomach (see Chapter VI) Frequently such emotional experiences were associated with nausea

6 *Mechanical Irritation* Moderately vigorous massage of the mucosal lining of the cavity of the stomach with a glass rod for 15 minutes, similar to that described in Chapter II, resulted in enhanced mucus production, but no acceleration of acid secretion or stimulation of contractions

Similarly, distention of the stomach with a balloon maintained for 15 minutes at a pressure of 25 mm of Hg and to a size of approximately 15 cm in diameter had no demonstrable effect on gastric function

7 *Change in Gastric Function Associated with Induced Pain* Intense pain was induced by placing the subject's hand in ice water and leaving it there for 5 minutes There occurred an associated elevation of blood pressure from a control level of 110/60 to 170/100 There was no detectable alteration of stomach contractions, although a very slight pallor and decrease in the rate of secretion of acid was noted

Similarly, when intense pain was induced by flexion and extension of the fingers while the circulation to one arm was occluded by a tourniquet for 15 minutes, there occurred no measurable change in gastric function during the period of ischemia and that following removal of the cuff except the first time the test was carried out On that occasion the subject was obviously alarmed by the procedure and fearful of its consequences While the tourniquet was in place the subject's face became pale, and the redness of his gastric mucosa decreased from a control level of 65 to 50 Acid output decreased correspondingly, but there was no change in the pat-

terns of the vigorous contractions which were occurring at the time Following the release of the tourniquet on this particular occasion, there occurred for 15 minutes a secondary hyperaemia of the mucosa to 70 associated with an acceleration of acid secretion

Comment These experiments serve to emphasize the importance of distinguishing between effects attributable to pain itself and those associated with the subject's reaction to the painful experience While a very slight vasoconstrictor effect, which might easily have been overlooked, was noted when the pain was accompanied by no special affect, when alarm and fright accompanied the pain the vasoconstrictor effect was greatly exaggerated and could not have escaped notice A discussion of the different factors involved in a subject's appreciation of a painful sensation and his reaction to it are discussed elsewhere[1, 2]

8 *Hypodermic Injection of Sterile Water* In order further to evaluate gastric changes which might occur as part of the subject's reaction to an unpleasant situation, the injection of 1 cc of sterile water hypodermically was tested

The subject disliked intensely being pricked by hypodermic needles Each time, the procedure provoked in him a reaction of resentment This may have been because, during his illnesses in the past, when administering to him a drug by the parenteral route the doctors often misled him regarding the effects of the injection

The usual slight anger and resentment accompanied his first sight of the needle The effects are shown graphically in Fig 16 A moderate transitory hyperaemia and associated accelerated secretion of acid occurred

9 *'Physical Exertion'* Moderately violent exercise involving rapidly raising and lowering one leg and both arms with

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7 *Change in Gastric Function Associated with Induced Pain* Intense pain was induced by placing the subject's hand in ice water and leaving it there for 5 minutes There occurred an associated elevation of blood pressure from a control level of 110/60 to 170/100 There was no detectable alteration of stomach contractions, although a very slight pallor and decrease in the rate of secretion of acid was noted

Similarly, when intense pain was induced by flexion and extension of the fingers while the circulation to one arm was occluded by a tourniquet for 15 minutes, there occurred no measurable change in gastric function during the period of ischemia and that following removal of the cuff except the first time the test was carried out On that occasion the subject was obviously alarmed by the procedure and fearful of its consequences While the tourniquet was in place the subject's face became pale, and the redness of his gastric mucosa decreased from a control level of 65 to 50 Acid output decreased correspondingly, but there was no change in the pat-

that the circumstances of an experiment and the patient's reaction to the procedure modify markedly the results obtained These factors must be taken into account by investigators when specific effects are attributed to drugs Detailed consideration is given to changes in gastric function associated with various emotional states in Chapter VI

11 *Influence of Acid on Gastric Secretion* Instillation of 20 cc hydrochloric acid in concentration of only 0 05 N exerted no discernible effect on gastric secretion

20 cc of 0 1 N hydrochloric acid, however, introduced into the stomach during a phase of moderately active secretion inhibited further acid production and stimulated the elaboration of mucus with the result that the acidity of the stomach contents was profoundly reduced Introducing 20 cc of 0 34 N hydrochloric acid into the stomach evoked an even more striking elaboration of mucus which within 15 minutes reduced by one-half the molar concentration of the acid By 30 minutes the gastric acidity had returned to its former level An illustrative experiment is shown graphically in Fig 17

12 *Action of Antacids* Several commonly used antacids were introduced directly into the stomach in order to determine (1) their neutralizing power, (2) the duration of effect, and (3) whether or not the agents affected the existing rate of acid secretion The usual observations of color and motor activity were made The stomach was emptied at 15-minute intervals and the amount of the contents measured A 5 cc sample was separated for analysis and the rest of the fluid was returned to the stomach The findings summarized here will be reported in full in a later publication [*]

Sodium Bicarbonate In 12 experiments amounts of sodium bicarbonate varying from 1 to 4 gm were introduced into the fasting stomach of our subject both during phases of accel-

a 2 lb weight in each, for 15 minutes while reclining on the table, brought about no detectable change in gastric function

Comment This type of physical exertion was deliberately selected because it was not accompanied by any special affect It is likely that competitive sports or other emotionally charged

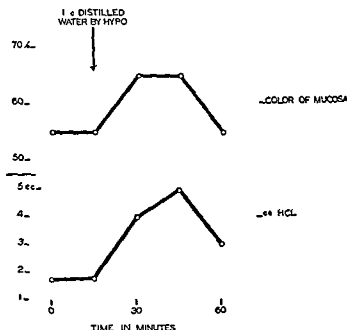


FIG 16 Changes following hypodermic injection of sterile water Reaction of anger and resentment

activities would be associated with alterations in gastric function

10 *'Mental Work'* The subject was asked to repeat digits and calculate simple sums without pencil and paper This task in our subject was inevitably associated with anxiety, embarrassment, and with feelings of insecurity He blushed both in his face and his gastric mucosa, and there occurred a moderate acceleration of acid secretion

Comment A great deal of importance attaches to the fact

that the circumstances of an experiment and the patient's reaction to the procedure modify markedly the results obtained These factors must be taken into account by investigators when specific effects are attributed to drugs Detailed consideration is given to changes in gastric function associated with various emotional states in Chapter VI

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Sodium Bicarbonate In 12 experiments, amounts of sodium bicarbonate varying from 1 to 4 gm were introduced into the fasting stomach of our subject both during phases of accel-

erated gastric function and during relative quiescence Following administration of the drug, the 'free' gastric acid fell usually to 0 within 15 minutes When the administration coincided with one of the phases of spontaneously accelerated gas-

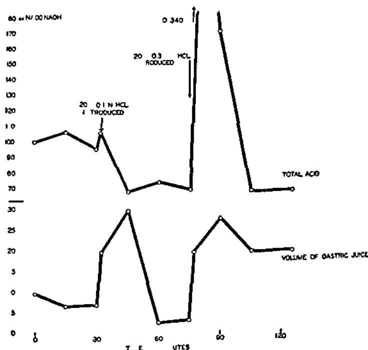


Fig 17 Acceleration of mucous secretion and inhibition of parietal secretion in response to the introduction of strong acid into the cavity of the stomach

tric function referred to in Chapter III, the 'free' acid at the collection a half hour after administration had usually risen to over 50 units When the drug was given during relative gastric quiescence, however, the 'free' acid remained below 20 for approximately one and one-half hours

Sippy #1 Tablets (sodium bicarbonate 2 gm, calcium carbonate 0 6 gm) Eight experiments were carried out using from 1 to 3 tablets of this mixture Results substantially similar to those noted after the administration of sodium bicarbonate

were obtained It was noted, however, that a quantity of the less soluble calcium carbonate adhered to the lining of the stomach and the duration of effect of Sippy #1 was approximately one hour longer than that of sodium bicarbonate in corresponding amounts

Sippy #2 Tablets (sodium bicarbonate 0 6 gm, magnesium oxide 0 6 gm) In 8 experiments in which 1 to 3 tablets were introduced into the stomach persistence of partial neutralizing effect up to 3 hours was noted Throughout this period bits of the powdered material could be recognized adhering here and there to the gastric mucosa

Aluminum Hydroxide Six experiments in which 30 cc of Amphogel * were introduced into the stoma showed a transitory neutralizing effect lasting less than 30 minutes when introduction of the drug was carried out during a phase of accelerated gastric function When vigorous contractions were absent, however the 'free' gastric acid remained below 10 units until the beginning of the next phase of accelerated gastric function which was often delayed as long as 2 hours

Comment It appears from the above that the neutralizing power of the various antacid agents depended upon the quantity of drug given and on the concentration of acid existing in the stomach at the time of administration The duration of their effect varied with the amount of motor and secretory activity present When vigorous contractions were occurring the antacid agents were quickly flushed out of the stomach, the gastric acidity returning to its former level relatively quickly In the absence of vigorous contractions however, partial neutralization of the gastric contents persisted for longer periods Although any acceleration of output of gas-

* Amphogel brand of 5 per cent aluminum hydroxide John Wyeth and Bros., Inc., New York City N Y

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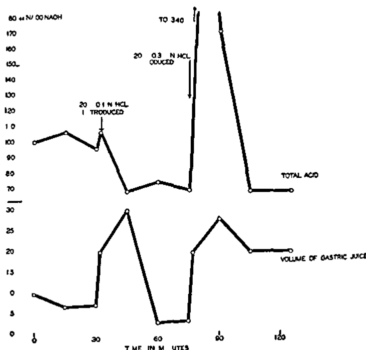


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mucosa, or a slight cyanosis Under these conditions there was little or no change in acid output

The inhalation of amyl nitrite regularly interrupted gastric contractions as soon as the drug was administered The inhibition was accompanied by progressive decrease in tone of the stomach wall The effects persisted until the inhalation was stopped, then the former tone was promptly regained and the original pattern of contractions was resumed in 2 minutes

14 *Nicotinic Acid* This drug was administered directly into the stoma in doses of 0 05 gm and 0 1 gm Frequently, no effects were noted When a flushing of the face occurred, however, there was a corresponding hyperaemia of the gastric mucosa and slight to moderate increase in parietal cell activity

15 *'Aminophyllin'* * Injection of 0 24 gm of theophyllinethylenediamine intravenously resulted within 1 minute in a slight hyperaemia of the gastric mucosa and increased secretion

16 *Ergotamine Tartrate* During a phase of accelerated gastric function, 0 0002 gm of ergotamine tartrate was injected intravenously A moderate pallor of the membrane ensued within 2 minutes and persisted for 45 minutes Associated with the pallor there was a decreased acid output (Fig 19)

17 *Atropine—Previous Studies* Most observers agree regarding the effects of the administration of atropine sulfate on the stomach[45] Amounts of 0 001 gm or more have been shown to reduce the volume of resting gastric juice They may abolish the stimulating effect of appetite and of the ingestion of food The stimulating action of alcohol was found to be markedly inhibited by atropine and that of histamine

* Aminophyllin brand of Theophyllin Ethylenediamine USP 0 24 gm per ampul G D Searle & Co Chicago Ill

tric acid necessarily reduced the neutralizing power of the drugs, no measurable effect on the secretory function of the stomach itself could be attributed to the administration of any of these agents in the amounts stated above

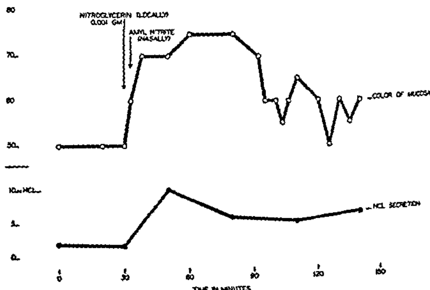


Fig 18 Influence of nitrites on gastric secretion and vascularity

13 *Nitrites* Fifteen experiments using amyl nitrite (0 3 cc) nitroglycerin (0 001 gm), or both were carried out Results were not uniform either with regard to subjective effects changes in blood pressure levels or changes in stomach function When a marked flushing of the face occurred, accompanied by a slight rise or no alteration of blood pressure, the gastric mucosa was seen to blush and an acceleration of acid secretion occurred This effect is illustrated in Fig 18 When a marked fall in blood pressure occurred, there was either no detectable change in the appearance of the gastric

product of the parietal cells, small though it was, was not being neutralized as much as before Bastedo[9] calls attention to this effect and warns that, because of it, atropine may not be a suitable drug to administer to patients with peptic ulcer

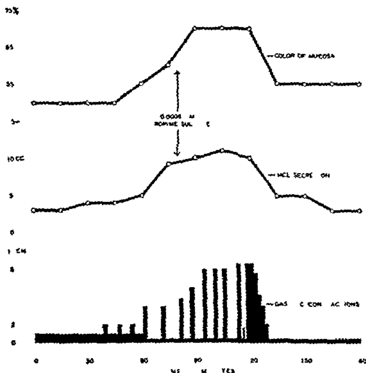


Fig 20 Lack of effect of 0 0006 gm atropine on gastric function

Previous observations[44] indicate that in dosage large enough to induce marked dryness of the mouth (0 001 gm) atropine sulfate inhibits gastric contractions for several hours

Observations Ten experiments were carried out to test the effect of ingested atropine sulfate on gastric function It was administered in doses varying from 0 0006 gm to 0 0024 gm Our results generally confirmed the experience of other ob-

less so The inhibitory effect on histamine was prevented by increasing the histamine dosage and then was re-established by raising the dose of atropine [7]

Investigators [5, 6, 8] have reported very little or no reduction of titratable acid after the administration of atropine Some

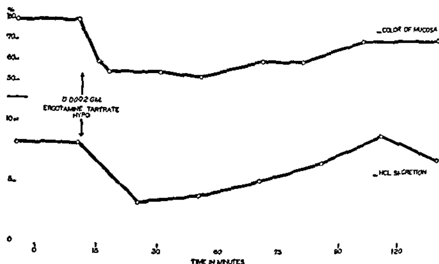


Fig 19 Vascular changes and changes in HCl secretion following injection of ergotamine tartrate

have noted a slight increase in acid concentration following administration of the drug

Actual measurements of parietal cell activity following atropine have not been reported, but it is apparent from the results of all observers quoted that although at times there occurred an increase in acidity, the marked reduction in volume of juice more than compensated for it and indicated that the output of the parietal cells was actually diminished The reason for the occasional rise in acid concentration despite the decreased output of acid was thought to be that atropine also effected a marked reduction of mucus secretion, and the

occurred Two hours after the administration of atropine, the subject ate a meal of chopped meat, milk, tea, and cake Six hours later it was still in his stomach He allowed it to escape through the stoma and noted that little or no digestion had occurred

18 *Effects of Epinephrine and Ephedrine* In order to establish whether or not the effects observed after atropine were due to uninhibited sympathetic effect or to the lack of vagal action, the effects of administering the sympathomimetic drugs, epinephrine and ephedrine were tested

a *Epinephrine Hypodermically* After a suitable base line was established 0 0005 gm epinephrine hydrochloride was injected hypodermically into the subject A minute later, there was a dramatic elevation of blood pressure which reached 210 systolic and 120 diastolic from a control level of 100 systolic and 60 diastolic Associated with this there was a pronounced pallor of the face, body, and extremities and an equally profound color change in the gastric mucosa as indicated in Fig 22 An intense headache at the vertex appeared at this time and persisted for a half hour Constricting praecordial pain and pain in the left shoulder were also noted, and there was associated difficulty in breathing The pain persisted for 20 minutes, and the dyspnoea to a diminishing degree, for 30 minutes After the initial effects of hypertension and pallor of the membrane were noted, there occurred a secondary hyperaemia of the gastric mucosa and with an increase in parietal secretion

b *Epinephrine Applied Locally* One drop of 1-1 000 solution of epinephrine hydrochloride was allowed to fall upon the exposed collar of gastric mucosa Within 30 seconds an area of whitish pallor had occurred After 5 minutes the original color began to return and in 20 minutes to half an hour the mucosa once again appeared normal 10 cc of a

servers Atropine was found to inhibit gastric contractions and secretion of mucus as well as parietal cell secretion The effect could not be consistently demonstrated, however, with doses smaller than 0 0018 gm This dose induced a marked and pro-

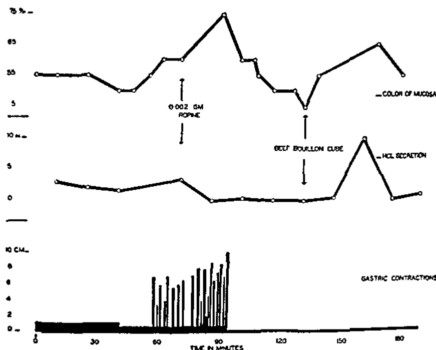


FIG 21 Marked effect of 0 0024 gm atropine on gastric function Note partial inhibition of beef broth effect

longed dryness of the mouth but no acceleration of the pulse or other side effects The dryness of the mouth appeared within 10-15 minutes, and the effects on gastric motor activity and secretion were evident within 20-30 minutes

Fig 20 illustrates the lack of effect after the administration of 0 0006 gm Fig 21 shows the marked effect of 4 times that dose One hour after ingestion of the drug beef broth was given The usual stimulating effect on acid secretion of this substance was markedly reduced, and no vigorous contractions

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1 10,000 solution of epinephrine were then introduced into the stomach through a tube during a phase of vigorous motility and active secretion The contractions stopped immediately, and pallor of the mucosa ensued with marked decrease in mucus and acid output Half an hour after ingestion of the

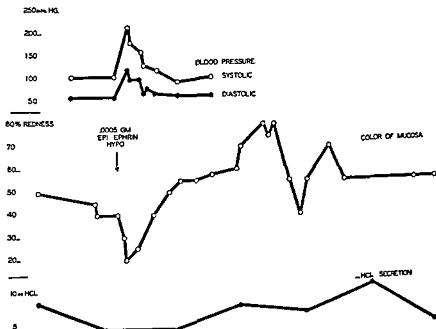


Fig 22 Effect of epinephrine administered hypodermically on gastric function

drug, however, the color had returned nearly to its former level, and secretion and motility were no longer inhibited (see Fig 23) No pallor of the face or elevation of blood pressure was associated with the introduction of epinephrine directly into the stomach

c *Ephedrine Hypodermically* After a suitable control period 0 05 gm ephedrine sulphate was administered hypodermically Tom seemed to resent being stuck with a needle

even more than usual No vasoconstrictor effect at all was noted, but instead, a marked blushing of the mucosa occurred with an acceleration of acid secretion These changes lasted for over an hour (see Fig 24)

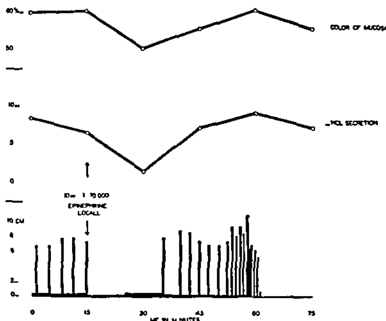


Fig 23 Effect of epinephrine applied locally

d *Ingested Ephedrine* On 2 occasions, 0 75 gm ephedrine sulfate was introduced directly into the stoma No significant changes in gastric function were detected

19 *Acetyl B-Methylcholine—Previous Work* Special interest attaches to the investigation of the effects of acetyl-B-methylcholine, since it has been shown that continuous infusion of dogs with acetylcholine as well as continuous vagus stimulation results not only in hyperacidity and hypermotility, but in ulcerations of the stomach and duodenum as well [10, 11]

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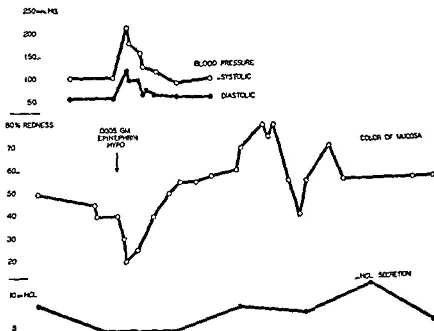


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B-methylcholine on gastric vascularity and secretion occurs in Fig 25

b *Effect on Motor Activity* The effect on motor activity was less reproducible than that on secretion and vascularity Out of 3 experiments with 0 2, 0 4, and 0 6 gm of acetyl-B-

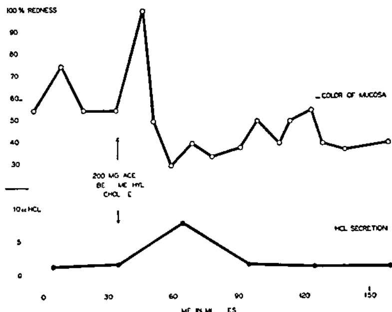


FIG 25 Effect of acetyl b methylcholine on gastric secretion and vascularity

methylcholine, respectively, vigorous contractions occurred in only the instance in which 0 4 gm was given They followed the ingestion of the drug by .0 minutes, and it was not possible definitely to assign the appearance of enhanced motility to the drug Two hours later however the subject had a loose watery stool This was unassociated with abdominal cramps

One regular accompaniment of the ingestion of acetyl B-methylcholine was a substernal tightness not unlike heartburn but which had less of a burning quality It appeared within

Observations—a Effect on Vascularity and Secretion On 10 occasions acetyl-B-methylcholine bromide was given by stoma in dosage from 0 1 gm to 0 6 gm The effects obtained did not appear to depend on the strength of dosage Increased

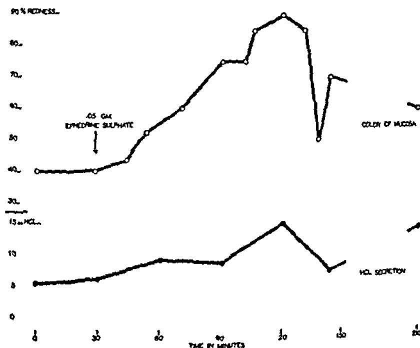


Fig 24 Effect of ephedrine on vascularity and secretion

parietal cell output began within 15 minutes of ingestion of the drug, but the extent of the increase was not uniform or predictable The magnitude of the increase varied from 50-200 per cent The maximum increase occurred 30-45 minutes after ingestion of the drug, and then the acid output quickly fell back to its control level Usually, the accelerated acid secretion was associated with a very moderate and transitory hyperaemia At times, however, the hyperaemia was marked A fairly representative tracing of the effect of ingested acetyl-

Observations—a Local Application of Pitressin 1 A drop of pitressin allowed to fall onto the exposed collar of mucosa brought about a marked blanching of the area in contact with the drug as did epinephrine In addition however the spot

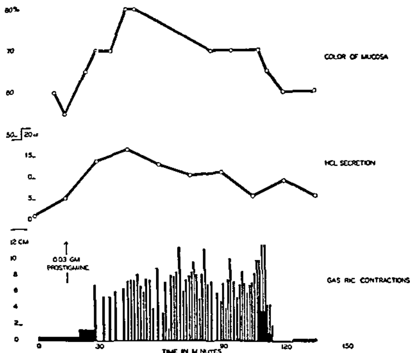


Fig 26 Effect of prostigmine on gastric function.

became flattened and depressed Within 5 minutes pin-point red spots appeared scattered through the area These gradually enlarged and became confluent Within 20 minutes these red areas had coalesced and the region had regained its former appearance

2 When 1 cc of pitressin in divided doses, each mixed with 10 cc of distilled water, was introduced through the stoma, there occurred a transitory pallor of the membrane

one minute of administration of the drug and lasted less than 5 minutes (It would appear in view of the data regarding 'heartburn' in Chapter IX that this sensation arises from the action of the drug on the cardiac end of the oesophagus)

20 *Prostigmine* 0 03 gm of prostigmine hydrobromide was introduced in pill form directly into the stomach Within 15 minutes the mucosa had become hyperaemic, and 5 minutes later vigorous contractions began and lasted for one and one-half hours This was the most prolonged, uninterrupted period of vigorous contractions recorded in any experiment During the terminal tetanic phase, the intragastric pressure rose to 30 cm of water, an unusually high figure Synchronous with waves of contraction of such magnitude were moderately severe cramps in the left lower quadrant of the abdomen

Not only was the motor activity of the stomach greatly increased by prostigmine, but so also was the activity of the parietal cells Acid output rose to 5 times the usual control level and remained elevated throughout the period of hypermotility

Within an hour and three-quarters after ingestion of the drug, the activity of the parietal cells had begun to subside, but comparatively little mucus was being formed since the concentration of acid as ascertained on titration was still unusually high In the following 15 minutes, however, a copious secretion of mucus occurred The volume of gastric juice was greater by twice than the preceding specimen, but it was extremely viscous and its acid concentration was less than half that of the preceding one (see Fig 26)

21 *'Pitressin'* * 'Pitressin' has been found to depress secretion when administered in small doses and to accelerate it when given in large ones [12, 18]

* Pitressin brand of beta hypophamine of posterior lobe of pituitary gland Parke Davis Detroit, Mich

rise in blood pressure and an associated pallor of the mucosa Twenty to thirty minutes following administration, however, there occurred a secondary hyperaemia of the mucosa, vig-

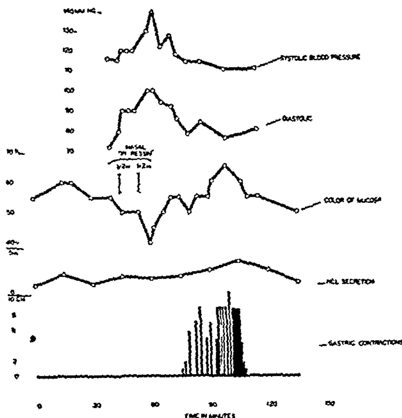


Fig. 28 Effect of nasal pitressin on stomach function

orous contractions and an acceleration of acid output (see Fig 28)

c *Pitressin Hypodermically* 0 2 cc of pitressin was administered hypodermically The effect was similar to that exerted by the drug when administered by nasal route but was less marked

which lasted 15 minutes and was associated with a decreased acid output Following this, however, there occurred an accel-

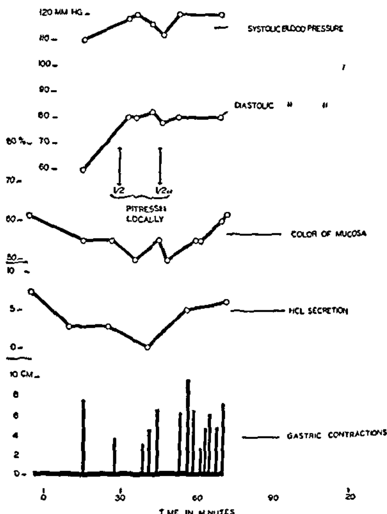


Fig 27 Effect of pitressin locally on stomach function.

eration of motor activity and acid secretion and a moderate hyperaemia of the mucosa (see Fig 27)

b *Pitressin Intranasally* 0 5 cc of pitressin was administered intranasally This was followed by a transitory sharp

tractions being inhibited and digestion delayed for 6 or more hours

6 Administered locally, epinephrine exerted a dramatic but transitory inhibitory effect on gastric vascularity, motor activity, and secretion Given parenterally, epinephrine and pitressin caused transitory pallor of the gastric mucosa, which corresponded in point of time to the period of elevated blood pressure Later, however, a secondary acceleration of gastric functions occurred This was especially true of pitressin, which regularly provoked enhanced motor activity and associated hyperaemia

7 Acetyl B-methylcholine induced temporary hyperaemia of the gastric mucosa and increased acid production Little effect upon stomach contractions was noted however, possibly because of the short duration of the influence of the drug

8 Prostigmine on the other hand exerted a profound influence on motility acid secretion and circulation All three were greatly enhanced for one and one-half hours following ingestion of the drug

For purposes of emphasis it is desirable to repeat that varying emotional states may be associated with profound alterations in gastric function (Chapter VI) Therefore, in the evaluation of the effects of drugs, the prevailing affective state of the patient at the time, the circumstances surrounding the experiment, and the patient s reaction to the mode and implication of the administration of the drug as well as his reaction to 'side effects' which the drug may induce, are of first importance

BIBLIOGRAPHY

1 Wolff H G J D Hardy and H Goodell Studies on pain measurement of the effect of morphine codeine and other

Summary and Conclusions It is apparent from the foregoing account that while a large number of physical and chemical agents were capable of influencing motor activity, acid secretion, and vascularity in the stomach, their actions might be modified or even reversed by effects associated with the subject's prevailing emotional state at the time or with his affective reaction to the experimental procedure itself

A consideration of the data recorded allows the following generalizations

1 The effects of environmental temperature and the ingestion of hot and cold liquids were so transitory as to be probably of little significance, although the accelerated gastric function which accompanied warming of the body following exposure to cold may be related to the stimulation of appetite, which is known to occur commonly at this time

2 No effects from tobacco smoking or physical exertion were noted

3 Vasodilator drugs in general caused an increased secretion of acid The effects of a single administration, however, were relatively transitory and even in the case of 0 0005 gm histamine were over in 45 minutes

4 Vasoconstrictors caused a diminution of acid output, but here again the effect was transitory and was generally followed by a secondary phase of hyperaemia and hypersecretion of acid

5 Atropine did not alter significantly gastric function when given in amounts smaller than 0 0018 gm In that amount and larger doses, however it decreased markedly the volume of gastric juice secreted but since both hydrochloric acid and mucus were reduced to a comparable degree, the concentration of acid in the stomach was not altered The effect on gastric contractions, however, was profound, vigorous con-

CHAPTER V

The Background and Personality of the Subject

OUR studies up to this point have dealt mainly with the stomach itself and with the indicators of its activity From here on, experiments take into account the situational factors prevailing at the time observations were recorded In addition they include correlations of alterations in gastric function with changes manifested elsewhere in the body, or apparent in the reactions and behavior of the individual as a whole Before these observations can be properly evaluated however, it is necessary to record a description of the subject with a detailed account of the facts of his experience and personality which have moulded his reaction patterns

General The subject was a small, lithe man of Irish extraction, he was 56 years old at the time the studies were undertaken His appearance was neat, but not overly so His manner was polite hearty with those he liked, but shy and cautious with strangers He talked in a spontaneous and straightforward fashion He was generally cheerful and buoyant but readily reacted to adverse circumstances with depressive reactions Easily offended and quick to anger, when aroused he was likely to indulge his feelings in swearing and physical combat

opiates on the pain threshold and an analysis of their relation to the pain experience *Jour Clin Invest* 19 659 1940
2 Wolff, H G J D Hardy, and H Goodell Studies on pain measurement of the effect of ethyl alcohol on the pain threshold and on the alarm reaction,' *Jour Pharm & Exp Therap* 75 38 1942
3 McGrath J F Stewart Wolf, and H G Wolff *Effects of various antacids on the stomach of man* (In preparation)
4 Keefer, C. S, and A L Bloomfield The effect of atropine on gastric function in man' *Arch Int Med* 38 303 1926
5 Polland, W S Effect of atropine upon gastric secretion after histamine stimulation *J Clin Invest* 9 319 1930
6 Porter, R T Studies of the effect of atropine on gastric secretion' *Proc Soc Exper Biol & Med* 29 504, 1932
7 Gray, J S The effect of atropine on gastric secretion and its relation to the gastrin theory *Am J Physiol* 120 657 1937
8 Atkinson, A J, and A C Ivy Studies on the control of gastric secretion 1 Drugs acting on the autonomic sympathetic system 2 Drugs acting as central emetics, *Am J Dig Dis & Nutr* 4 811, 1937
9 Bastedo W A The value of atropine and belladonna in stomach disorders' *J A.M A* 106 85 1936
10 Manning G W, G E Hall and F G Banting Vagus stimulation and the production of myocardial damage,' *Can Med Assn J* 37 314 1937
11 Hall G E G H Ettinger, and F G Banting An experimental production of coronary thrombosis and myocardial failure, Ibid 34 9 1936
12 Dodds E C R L Noble R W Scarff and P C Williams Pituitary control of alimentary blood flow and secretion Changes in the stomach produced by the administration of posterior pituitary extract *Proc Roy Soc* London Series B 123 22 1937
13 Cutting W C E C Dodds R L Noble and P C Williams Pituitary control of alimentary blood flow and secretion The effect of posterior pituitary extract on the alimentary secretions of intact animals *Proc Roy Soc* London Series B 123 27 1937

CHAPTER V

The Background and Personality of the Subject

OUR studies up to this point have dealt mainly with the stomach itself and with the indicators of its activity From here on, experiments take into account the situational factors prevailing at the time observations were recorded In addition they include correlations of alterations in gastric function with changes manifested elsewhere in the body, or apparent in the reactions and behavior of the individual as a whole Before these observations can be properly evaluated however, it is necessary to record a description of the subject, with a detailed account of the facts of his experience and personality, which have moulded his reaction patterns

General The subject was a small, lithe man of Irish extraction, he was 56 years old at the time the studies were undertaken His appearance was neat, but not overly so His manner was polite, hearty with those he liked, but shy and cautious with strangers He talked in a spontaneous and straightforward fashion He was generally cheerful and buoyant, but readily reacted to adverse circumstances with depressive reactions Easily offended and quick to anger, when aroused he was likely to indulge his feelings in swearing and physical combat,

or in retaliatory measures and minor acts of vengeance Thus, he usually gave expression to his feelings of hostility rather than silently bearing grudges His behavior was made to conform to a set of rigid standards and his code of ethics was high He put a great premium on self-sufficiency and self-respect His gastrostomy constituted a constant threat to his ideal of physical integrity and fitness, as well as to his desire to 'belong,' and he took elaborate pains to keep it secret This tendency occasionally led him to suspect that people were following him with their eyes and talking curiously about him His schooling had stopped at the grammar grades and his general information and intellectual abilities were consistent with that level He was alert, resourceful, and facile with his hands His judgment was often colored by his stubbornness and inflexible standards of propriety

Home Environment He was born in the outskirts of New York City in 1885, the third of four children of an Irish Catholic mother and a Protestant father The latter worked as a boss mechanic, had steady employment, and provided adequate necessities as well as a few modest luxuries for his family He was punctilious and moderately rigid but a companionable parent, who went fishing and walking with his sons The mother was very obese, and though 'sickly' she dominated the household She was a devout Roman Catholic, demanded perfection in deportment from her children, but required little of them in the sphere of education For example, the desirability of making good grades in school was never stressed The patient was not allowed to read the newspaper until he was 15 years old His parents considered what they vouchsafed to him adequate general information They made no special concessions to him because of his gastrostomy

The accident that necessitated the operation occurred when

Tom was 9 years of age A neighboring saloonkeeper had offered his father some hot clam chowder The father carried it home in a chilled beer pail, which happened to be the closest thing at hand He deposited it in his kitchen and went out A few seconds later, Tom, who was thirsty from playing outdoors, came into the kitchen and seeing the pail he grasped it by the top which was still cold Thinking he was sneaking a draught of beer, he took a very large mouthful of the extremely hot liquid He was afraid to spit it on the floor, because he feared reprisals from his mother, so he swallowed it For an instant, he felt an intense burning sensation in his mouth throat and abdomen and then he fell unconscious onto the floor His mother, who was ill upstairs heard the crash and came down From then on she assumed complete charge When he was finally released from the hospital after his gastrostomy operation it was she who fed him all his meals through a tube No one else knew how The father gave no evidence of feelings of guilt for having brought home the chowder in a beer pail, nor was the patient blamed for his intention to drink beer on the sly The whole incident was accepted simply as a catastrophe and for weeks the worried parents made Tom an object of special solicitude After his release from the hospital, however he was made to assume his former status with the other children and got no preferential treatment

The parents were happy together Their difference in religion never constituted a problem as far as the patient was aware The father never went to church, although he was sympathetic with his wife s devout behavior He was glad to have the children brought up Roman Catholics and he cooperated in prodding them all to get off to church on time He rehearsed with them their catechisms and supported the

mother's emphasis on the necessity of their participating in the various sacraments at the proper time The parents respected each other, but made no show of affection Emotional display except for anger was not tolerated in the home, and Tom was 'ashamed' to cry He had a favorite spot in the woodshed where he used to cry once in a while, but he rarely felt rebellious, because his parents' discipline seemed to him scrupulously just. Elaborate precautions against favoritism were taken When one of the four children committed an offense, all were held responsible and all were punished The punishment was meted out by the mother and it consisted of lashing with a leather strap and confinement in one's room

The father gladly gave over the administration of the house to his more forceful spouse and he supported her decisions Even he was not exempt from her stern measures of disapproval at times One day he took Tom into a saloon Tom stepped into the washroom, and when he came out he saw two women sitting at the table with his father That evening he related the story to his mother with the result that the father became an object of disapproval for two weeks

Tom had a fear and a love for his mother such as he had for the Lord One day she called him to her while he was out swinging in the backyard He stopped the swing as soon as he could, but not quickly enough for her, so she came out of the house and lashed him with a leather strap across the face The end of the strap caught Tom in the left eye and caused marked oedema and discoloration His mother was obviously frightened and ashamed of what she had done, but she said nothing That evening when his father came home, he inquired of Tom what had happened Tom said he had run into a door in the alley When the children were well behaved and things went smoothly at home the parents were cheerful,

friendly, and generous Holidays were especially festive and everyone was given presents

Personal problems were not discussed much at home, but Tom felt that he could approach either his father or mother He placed more confidence in the latter 'If mother told you to do something you thought was impossible she'd insist on getting it done, and if you couldn t do it, she'd just as soon show you how Father would just let it go'

Siblings Tom had a sister two years older than himself a brother one year older, and another brother ten years younger He never cared much for any of them, except his sister His mother died when Tom was 14 His sister took over the running of the house and helped Tom when he was ill If she lived 100 miles away and I didn t have the train fare, I'd walk over to see her'

The older brother was a rather detached individual, bigger and stronger than Tom and often bullied him This brother married without the consent of the family and was consequently not allowed to return home His wife never cared for Tom and therefore he later saw very little of them

The younger brother was of a rebellious nature and spent much time in a reformatory because of truancy Later on Tom did a great deal to help him, but he felt his efforts were not appreciated They gradually grew apart

Neither of his brothers could stand the sight of Tom s gastrostomy without getting sick He ate with his sister however and with her husband after her marriage

Tom went to work after completing only six years of school He held several jobs requiring semi-skilled labor, married at 28 and had 2 children The first died in infancy He got on well with his wife was seldom drunk and never jailed During the years of economic depression he was hard put to

it to make ends meet Finally, he was able to find a measure of economic security as a worker in our laboratory at the age of 56

Reviewed below are some of the factors which shaped the character and reactions of our subject

Mother's Death From the time of the operation until she died six years later, Tom's mother fed him through a tube No one else, including Tom, could accomplish the feeding He was terrified when she was obviously dying, and he practiced feverishly at feeding himself It was then that he devised the method of chewing the food before putting it in his stomach, and it was not until then that he really began to gain weight and become robust His feedings before that had been fluid and he had a persistent diarrhoea unless he took bismuth powders

Everyone except the oldest son went to pieces when the mother died For two weeks the family was scarcely able to get from one day into the next Tom felt that he had lost his anchor Eventually the sister filled the mother's place in Tom's emotional life, but in a slightly different way He was devoted to and dependent on her, but not awed by her

Father's Death When Tom was 21 his father died as a result of an accident in a railroad yard where he was working One of his legs was crushed and partially severed Tom arrived at the scene of the accident shortly after it happened He felt that an inordinate delay in providing medical care had compromised his father's chances of survival Although he felt bereaved at his father's death, he reacted less violently than he had to his mother's Apparently well-directed legal proceedings failed to recover indemnity from the railroad Following his father's death, he lived with his sister and her husband until he married at 28

Social Development As a child Tom was an outgoing, aggressive, athletic boy Although he got into a great many fights he was not exactly belligerent In fact, he made friends easily and won the loyalty of his comrades by his fitness and good sportsmanship For this, he was rewarded by being selected often as captain of the team

Need for Physical Fitness The reaction of his associates to his gastrostomy was one of sympathy, amounting at times to patronage They were never contemptuous, never chided him for his handicap They rather favored him, tried to give him easy positions on the teams and many of them expressed their wonder that he was able to carry on in the face of such a staggering handicap Tom heartily resented this display of solicitude and their well meaning pity provoked him to combat, until they learned to accept him as one of their number without reservation Thus his gastrostomy did not curtail his athletic activities or his gregarious tendencies but it did give him a feeling of insecurity, because it set him apart from other people, and it was not altogether compatible with his ideal of bodily integrity and fitness Consequently he elaborately concealed his defect, and kept it secret even from his friends He was not overreactive to pain, but he felt he could not tolerate being sick or being near others who were

Youthful Resentment One of his early vivid feelings of resentment was directed against a boy playing football on the opposing team Tom had fallen on a 'free ball,' and the other boy had piled on top of him with a display of unnecessary roughness Tom had a complete herniation of his gastric mucosa and an operation was necessary to reduce it He fought a battle with that boy when he was released from the hospital

Relationship to Physicians Tom felt a blind confidence in the doctors who looked after him in the hospital at the time

of his first operation He is intensely grateful to them and attributes to their wisdom and foresight his ability to have carried on in life in many ways like an average man and be gainfully employed After discharge, however, he visited a doctor in the out-patient department, whom he had not seen before He felt that this new doctor was curt and unsympathetic Tom was impatient of the aggravating problems which arose from time to time regarding the proper functioning of the fistula *One day his doctor told him sharply that everything* possible was being done for him This peremptory treatment offended and angered Tom He felt rejected and more than ever set apart from others He never returned to the out-patient department At 17 years of age he sought aid at another hospital, thinking that a properly designed belt might help hold the stomach contents in He noted, however, that the doctor who saw him appeared more curious about the fistula than interested in solving his problem, so he stepped off the table and left the clinic before the examination was completed He took *the opportunity of disappearing when his* doctor stepped from the examining room to call in some colleagues to see the lesion It seemed to Tom that all doctors whom he saw from then on were more interested in his fistula than in him He became increasingly suspicious of physicians in general From the age of 17 to 53 Tom never allowed a doctor to examine his abdomen He was sick with minor illnesses several times during this period, and he consulted many doctors, but despite their entreaties, they were permitted to examine only his head and chest

Once he was hospitalized for four days following accidental carbon monoxide poisoning He steadfastly refused to allow the doctors or any of the hospital personnel to look at his gastrostomy opening He declined even to feed himself while in

the hospital His suspicion was coupled with anxiety that the doctors might persuade him to submit to operation, which might result in spoiling the serviceability of his fistula There was some foundation for this fear, since the surgeon who reduced the herniation of his mucosa, on the occasion referred to earlier, did so by enlarging the opening and making a notch in the collar of redundant mucous membrane This allowed the gastric juice to escape and digest an area of skin on the abdominal wall This denuded area has remained a source of discomfort to him ever since

Tom became headstrong and independent, often overruling expert advice on matters on which he was not competent to give an expert opinion For example, one day he sustained a deep laceration of the finger, which nearly cut it off The first doctor whom he consulted advised amputation He refused and consulted four other doctors These either recommended amputation or suturing The patient steadfastly refused such treatment however for he had set his mind against losing his finger or having stitches taken in it Finally he found a physician who was willing to dress it with adhesive tape only The member healed uneventfully and Tom felt vindicated On another occasion when his wife required operation for removal of a myoma uteri, he called in three doctors before he would accept the diagnosis

He never actually gave himself into a doctor's hands until 1939, when he was profoundly debilitated by loss of blood from chronic haemorrhage from his stoma He had been doing ditch digging and was wearing a tight-fitting gauze dressing over his defect The dressing excoriated the edges of the exposed mucosa and caused them to bleed almost continuously His wife had been trying vainly to prevail upon him to seek medical help Finally he agreed At that time he had hardly

enough strength to stand His wife begged him to take a taxi to the hospital to conserve his strength Tom was contemptuous of the idea, however, and walked part way and rode the rest of the way to the hospital on a bus He just barely made it When he arrived he allowed the fistula to be examined for the first time in over 30 years The doctor corrected his trouble by resecting the tiny buds of tissue, which were the source of his bleeding He also resected a considerable portion of the redundant mucosa, but against the patient's expressed desire This extra tissue had served as a cork for his stoma to hold in the food after meals After the loss of this tissue, Tom felt that the corking action was less effective, for he often lost part of his meal, and at times a good deal of acid gastric juice escaped on his abdominal wall Thus another problem was added to his already difficult task of managing *the stoma, and his anxiety regarding 'doctors' was increased*

It was approximately two years after this experience that the task of persuading him to become a subject for investigation was undertaken It took four months to create adequate rapport with the patient Finally, Tom was convinced of our interest in and solicitude for his welfare, both physical and economic It then seemed to him that the study of the fistula was not merely an object in itself, but might afford a means of improving his status and enhancing his security A workable plan was devised, which could be reconciled with his self-respect He was given a job as assistant and handy man in the laboratory Those offices he discharged in the afternoons In the mornings he came to the laboratory without having eaten, and observations were made on his stoma with an eye to improving its function by simple modifications of routine An express promise was made that surgery would not be considered

Within a few months Tom developed a devotion and dependency on one of us (S W) akin to that which he had had for his mother He had not been able to enjoy such a feeling of personal security since her death His sister never quite provided it, and with his wife he always had to assume the role of protector He could not discuss his thoughts or problems with her frankly, because of her ready anxiety He had therefore, not been accustomed to confide his troubles and secret thoughts to anyone, until he acquired this new attachment Then he began to do so with evident relief

Interest in Women and Marriage Tom had always liked company and in his youth he had associated freely with girls but he avoided seriously involving himself because he was afraid to tell them about his gastrostomy When at length, at the age of 28 his desire to marry was strong enough, he selected a widow aged 33, with three children—two boys and a girl aged 8, 9 and 11 I could have gotten plenty of younger ones but I was afraid a younger woman might eventually get disgusted with the way I feed and throw it up to me I couldn t stand that he said He felt that he was a bargain for her even with the defect in his abdominal wall She was plain but companionable and loyal Despite the lack of erotic motivation he was greatly relieved by her acceptance of his proposal and he entered marriage happy that he 'belonged and that nothing now set him apart from ordinary mortals He had no special desire for children but some of his untutored friends had expressed doubt of his ability to reproduce because of his peculiar handicap Therefore he was determined to have at least one child

Life as Head of His Family In creating a family circle he emulated his mother established himself as head and took responsibility for the behavior of the other members He

trusted his wife thoroughly He liked her cooking and her company, and he approved of her in private and in public His stepchildren he treated well, but they were jealous of him at times, and especially so of their stepsister, who was born two years after their mother's marriage to Tom The discipline of his stepchildren Tom left largely to his wife The upbringing of his own daughter, however, was his own personal charge, and he applied the familiar rigid standards of his parents Rarely did his wife take exception to his administration of justice On the whole, she trusted and followed him

Work Record Tom had started working at the age of 10 as a plumber's helper He did not want any further schooling and his mother allowed him to go to work because his father was ill with pneumonia and the family income was cut off for the time After five years he quit the job, when he was required by the boss to fulfil a demand which he considered inordinate

His second job was at a theater, and he held it until the enterprise broke up 16 years later He had worked up in the organization to stage manager and assistant superintendent

This was followed by a brief period of work as a repair man on top of elevators in a large office building He quit that after a week because one of the operators was regularly intoxicated, and Tom felt that his safety was jeopardized by the man's drunkenness

He quickly found other work, however, in a hops processing company, which later failed because of the advent of prohibition

Shortly after this, he began to work for a clothing manufacturer as foreman and repairer of machines He enjoyed the work, but was forced to quit when the factory moved to another locality

Following this, he worked as a skilled laborer in a real-estate repair company He loved this variegated work as machinist, paperer, plasterer roofer, etc Like the theater job it gave him an opportunity to exercise his initiative and manual dexterity For 12 years he was happy in this job and then animosity grew up between him and the foreman, who was jealous of favors which the employer conferred on Tom and of the informal friendly relationship between the two The foreman continually took measures to reflect an unfavorable light on Tom's work Once he complained to the employer about Tom's performance with the lathe He called the employer in to witness his work after first deliberately setting Tom's lathe off center Tom retaliated with similar underhand methods, such as watering the foreman's grease and mixing up his shipments

Finally a question of veracity arose between himself and the foreman The boss did not know which to believe He preferred to dismiss the incident, but Tom insisted that he choose between the two of them The boss liked and trusted Tom but the foreman had saved his life by throwing a blanket around him once when his clothes caught on fire Furthermore he had recently lent the foreman $6,000 to buy a house and was deducting payments from his salary check The boss chose the foreman and Tom quit the job

Reaction to Financial Insecurity Later on Tom worked for a canning company that subsequently failed and finally in the sewer division of the W P A It was while at this hard physical work at the age of 53 that his stoma became excoriated and began to bleed This led to invalidism and hospitalization and was followed by a prolonged period of convalescence It seemed impossible to get another job He felt frustrated and humiliated beyond words He was so poor that he

and his family had to live in a near hovel He shunned his old acquaintances and kept his address secret

Money alone could not cure him It was self-respect he desperately needed He shunned offers of subsidy to exploit scientifically his gastrostomy He refused to allow his wife to work and support him He had hesitated to undertake marriage in the first place, because 'If I couldn t support my family, I'd as soon jump off the end of the dock' It had become a source of great pride to him that in 29 years of married life his wife had never had to seek employment. He accepted relief money reluctantly, because he could not bear to see his wife and daughter starve He was prepared to do any sort of work, however lowly and disagreeable, and at any salary He was finally induced to come to the New York Hospital by the offer of a job

Having got the job he worked at it furiously He dreaded the thought of losing it, for he felt he might never get another One night when the question of how long it would last came up in a discussion with his wife, he became so agitated that he got no sleep at all When he was assured the following morning that his job was to continue indefinitely he was tremendously grateful

He reveled in his new-found security He was once more a self-respecting father of his family He needed that feeling and he needed the approval of his close associates

Need for Justification in the Eyes of Those He Held in High Regard On moving his family into the new house for which he had taken responsibility they found it infested with cockroaches His daughter said 'Is this the dump you brought us to? I'll never bring my friends in here' His wife too was disgusted, and he worked feverishly to get the place clean, but even after a thorough scrubbing with lysol and

ammonia, the vermin were still present He felt guilty and alone—he wanted someone to share the responsibility with him He had effected an armistice at home by promising to move out if he could not exterminate the pests in three weeks He refused an offer to have it done by a professional exterminator He was willing to accept the materials but insisted on doing the job himself Within the allotted three weeks the pests were entirely eradicated

Standards It is clear from the foregoing that the subject's ethical standards were high and rigid Once when, against his orders, his daughter went automobile driving with some boys and later denied having done so he struck her That was the only occasion on which he ever did that, and following the episode he experienced profound feelings of guilt Recollection of the incident is still troublesome to him

His aesthetic experience was meager and he has no interest in graphic arts or music His material needs were small His ethical goals were those of an orthodox Roman Catholic He was intolerant of weaknesses in himself and others He was conscientious, devoted to duty but not actually perfectionistic His conscience required adherence to his own rigid standards rather than to any which others might try to impose on him His ideals were inflexible but did not exclude kindliness, and he had no tendencies to hobbies or fanaticism His attitude towards state and society was sober and conservative There was no strong need to rationalize no exaggerations no dramatizations or hypocrisy

He saved a portion of his income to gain economic security but was not avaricious or penurious He had no marked need for pleasure nor had he an ascetic attitude His need for justice was strong He was rarely needlessly depreciatory and was usually quick to recognize the value of others His reli-

gious observances were automatic rather than devout He did not feel that divine intervention figured perceptibly in his life He accepted the doctrines of the church without challenge and he attended church and observed sacraments regularly

Sexual Drive Little is known about childhood influences on his sexual development In his family there seems to have been strict taboo on sexual discussions In adolescence, the patient received sexual information from other youngsters and indulged in erotic fantasies without masturbation After his twenty-second year, he had satisfactory intercourse on infrequent occasions with several women Unlike many of his friends, he scrupulously avoided discussion of his sexual exploits He met his wife when he was 27 and more on her initiative than his, he married her at 28, their only child being born two years later Intercourse was only moderately satisfactory and his sexual desire decreased rapidly after about three years, coitus occurring only once every five or six months His strict code did not permit him to live out his desires for promiscuity Sexual fantasies have played merely a minor role during the last ten years During his whole adult life there seems to have been less sexual drive than average

Affection It has already been pointed out that Tom's affection for his mother involved little warmth of feeling He depended on her completely and looked to her for judgment and guidance In return he was well behaved and loyal, but he really gave very little of himself in the relationship A show of affection was discouraged by his parents From his sister he got companionship and haven and gave loyalty in return He selected for a wife a mature woman who would make a respectable home and deserve his labors Nowhere in his life did he give himself to the fullest extent emotionally

An important reason for this reluctance may have been 'the way I feed,' with its associated feelings of insecurity and fear of being humiliated This caution was accentuated by his sister s attitude She openly believed that it was hopeless for Tom to expect a 'decent girl' to fall in love with him, considering his handicap Tom did not resent her expressing herself in that way, because he felt that her object was to protect him from disappointment He did desperately want to prove her wrong but hesitated to try One reason I picked out my wife, he said, 'was that she had children, and had washed diapers My bandages were nowhere near as bad as a baby's diapers'

Just once, Tom felt that he had really 'fallen in love' He was 21 at the time He knew the girl in all only a few weeks Despite his inhibitions, and his sister's gloomy attitude, he let himself go in his feeling for her He recalled the experience in these words 'She was beautiful and very gay I liked to be with her, and she seemed to understand just about everything One day she had to go away, and then she disappeared and I never heard of her again After she left I couldn t eat for three weeks' He had planned to tell her about his gastrostomy, but he had not done so as yet He does not know but he feels that it is possible that she disappeared because she heard about it from another source

Eating Tom s appetite for food and drink was average and he had no special cravings One effect of his gastrostomy was to rob him of the oldest and most established social amenity that of eating and drinking in company Since he kept his handicap an elaborate secret he was continually being invited by friends to take a meal or a cup of tea or a drink with them It was necessary for him each time to tell involved falsehoods in order to avoid making a rude refusal He hated

eating alone, and he took great comfort and enjoyment in sharing mealtime with his wife and daughter or with his sister

The children of Tom's stepdaughter and his sister are growing up aware of the manner in which he has to eat and are not disturbed by seeing him eat However, he has never allowed the husband of either his stepdaughter or his sister to see him take food, although they know of his difficulty Tom's world of people was divided into those with whom he was and those with whom he was not able to eat With the former he was frank and intimate, but with the latter detached and often suspicious After our studies had been in progress for half a year, Tom invited our technician to eat lunch with him He undertook this step with grave doubts and apprehension She accepted readily, however, and ate and chatted with him in an easy, natural manner She did not appear in the least repelled, and in fact, expressed a desire to continue the practice Tom was jubilant 'She's a swell girl, you know She doesn't mind the way I feed'

Fantasy Tom had few dreams at night and was rarely able to remember them He spent little time in daydreaming and fantasy His fantasies all began with reminiscences of youthful experiences He reflected upon the boys he knew in school One became a fire chief, one a captain of police and another a magistrate He envied their easy security and positions of distinction He felt that he would be in a similar position had it not been for his handicap 'I always wanted to be a cop for some reason' A second pattern of fantasy involved recollection of the many beautiful girls he knew, and how so many of them invited his attentions 'I could have had plenty of them' he says to himself, and then concludes on this note, 'Well I don't think I did so bad Not a one of them would have stuck to me the way my wife has She's a real

sport.' A third pattern includes a recapitulation of all the jobs he has had 'There's not a trade I couldn t do, but I never had a chance to learn them thorough I would have been a master mechanic or plumber now and making big money in defense, but if one of those company doctors saw this hole, he d faint Why, he wouldn't be able to get me out of there quick enough'

Social Needs and Adjustment to the Group Despite the rigid make-up of his character, his suspicions of other people, and his unwillingness to compromise, Tom preferred to be in a subordinate position He disliked making decisions which affected those outside his family and when this was necessary, he was constantly tense anxious and filled with misgivings and doubts He was happiest under leadership which he trusted and could feel dependent on In relation to those about him he desperately wanted to 'belong but was often shy, ill at ease, and concerned about the impression he made

He was reserved, and did not like to confide things but did so with evident relief when firm rapport was established He took advice and criticism only when he admired and trusted the giver Otherwise, he resented it

He had many superficial friends no close ones because he did not like to become involved in their problems, or to have them involved in his He belonged to no lodges or fraternal organizations and he had no special clique of men friends He spent most of his time working, or resting about his house He liked pet animals of all sorts and frequently had them about him Social life was limited to occasional calls which he and his wife made on friends and relatives

Summary and Personality Synthesis Essentially, Tom was shy, sensitive proud stubborn and slightly suspicious He was fun-loving but very conscientious His early training was

strict and his ethical standards were high He had a horror of disgrace or stigmata of any kind An outstanding threat to his physical and emotional security was the gastrostomy, which resulted from his accident He tried to compensate for the handicap and fought any disposition on the part of his friends to set him apart The death of his mother, on whom he was dependent, increased his sense of emotional insecurity His feelings of inadequacy were accentuated further by the fact that he was denied the social experience of eating in company He became shy and suspicious in his personal dealings, and developed a special *méfiance* of doctors Therefore, he lived a moderately shut-in existence, but he was not given to fantasy

For a wife, he selected a woman five years older than himself She seemed brave and dependable

Tom was averse to being conspicuous and was wary of responsibility outside his family circle He was anxious to belong to a group, but needed to be at once self-sufficient and subservient to leadership As frequent events in his life threatened his security, he often experienced short periods of anxiety and resentment Generally, he gave expression to his feelings rather than suppressed them

On the whole, his adjustment to life was adequate He was a useful citizen and since the material demands of all concerned were small, he was able for the most part to be a competent and self-respecting *pater familias*

CHAPTER VI

Changes in Gastric Function in Reaction to Various Situations and Accompanying Emotional States

THE fact that emotional disturbances are associated with disturbances in digestive function has been known for centuries. The familiar 'empty' feeling in the pit of the stomach accompanying fear, the anorexia, nausea, and vomiting which are often encountered at times of marked anxiety, are well known. Objective evidences of altered gastric function during emotional stress have been observed by several investigators.[1,2] A quantitative approach to the alterations, however, together with a detailed analysis of the settings in which they occur, has only been attempted recently.[4] It was with an eye to ascertaining whether or not disturbances in stomach function which are associated with adverse emotional states might have some bearing on the production of lasting and serious lesions of the stomach that this study was carried out on our subject.

Method. Observations of stomach function were made after the manner already described (Chapter II). Simultaneous records were made of stomach contractions, secretion, and vascularity. Also, salivary secretion was estimated by having the

patient empty his oesophagus at the beginning of the experimental period and again at the end The amount which accumulated during this period was then measured At the same time, careful note was made of the patient's mood and the content of his thoughts and preoccupations These data were collected during the experiments as well as at separate daily interviews An attempt was made to classify the dominant emotional and other reactions as pleasurable excitement, affection, doubt, fear, frustration, tension, guilt, sadness, anxiety, hostility, resentment, disgust None of these existed alone, but usually it was possible to recognize one as the dominant affect The emotional reactions were then correlated with the various measurements of gastric function

Emotionally charged situations were not experimentally induced but spontaneously occurring life problems and conflicts were utilized Some of these involved situations arising from time to time in the laboratory Others occurred in the setting of the subject's home life His reaction to each of these experiences was evaluated in the light of his personality pattern described in detail in the previous chapter Thirty-four observations of stomach function accompanying several different affective states were made From these, illustrative examples will be presented

The terms 'fear' and 'anxiety' have been used by various authors to imply different meanings In this communication fear is used to indicate an emotional reaction to danger in which feelings of alarm, terror, and helplessness verging on abjection dominate, 'anxiety,' a reaction to danger in which defeat threatens, but in which resistance survives It is commonly associated with hostility, resentment, guilt, and conflict

Observations 1 *Feelings of Appetite* Appetite, discussed in Chapter III, is introduced again here since it is a mental state during which alterations in gastric function occur The fol-

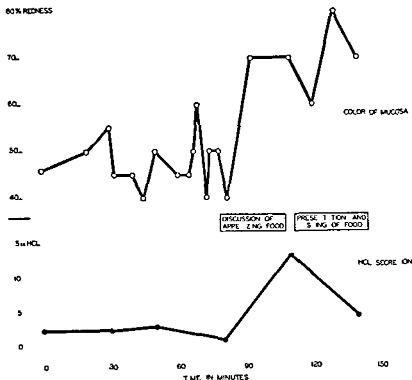


FIG 29 Response of the stomach in terms of vascularity and acid secretion to stimulation of appetite

lowing experiment illustrates the response of the stomach in terms of vascularity and secretion to the mere discussion of delectable dishes without the sight, smell or taste of food

Fig 29 illustrates the findings graphically During the control period the color of the mucosa and the rate of acid secretion were relatively constant At the point where the discussion of appetizing food was begun the membrane became

redder and the output of the parietal cells increased Actually tasting the food added little to these effects

2 *Alarm Reaction Involving Fear* Sudden fright occurred one morning during the control period of accelerated gastric function, when an irate doctor, a member of the staff, suddenly entered the room, began hastily opening drawers, looking on shelves, and swearing to himself He was looking for protocols to which he attached great importance Our subject, who tidies up the laboratory, had mislaid them the previous afternoon, and he was fearful of detection and of losing his precious job He remained silent and motionless and his face became pallid The mucous membrane of his stomach also blanched from a level of 90 to 20 and remained so for 5 minutes until the doctor had located the objects of his search, and left the room Then the gastric mucosa gradually resumed its former color (see Fig 30)

Acid secretion, too, decreased during the period of collection which included the marked pallor of his mucosa

3 *Depressive Thoughts* Sadness, discouragement, and self-reproach were found to be associated with prolonged pallor of the stomach mucosa and hyposecretion On one occasion it was noted that an actual inhibition of the usual effect of beef broth on the gastric vascularity and secretion occurred during a period of mood depression

The subject and his wife had long been desirous of moving their residence, which in their opinion was in an unpleasant neighborhood For some time they had been eager to acquire a particular house in another district which seemed perfectly suited to their needs They knew that the current lease would not be renewed and they had been given a verbal option on the lease by the landlord Mainly through their own negligence, however, they were not on hand when the new lease

was due, and the house went to someone else for less money than our subject and his wife were willing to pay The morning after this discovery he was downcast uncommunicative,

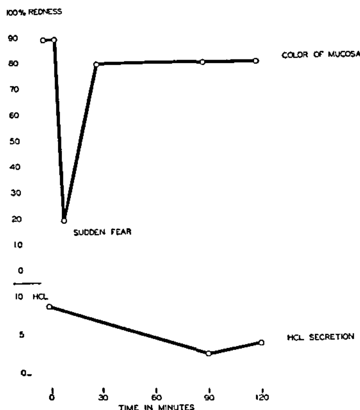


FIG 30 Changes associated with fear

and difficult to approach He could not be induced to reveal the cause of his sadness until several hours later Then he was questioned in detail with regard to his feelings in the morning His mood was sad and resigned He felt defeated and had no desire to fight back and establish his own prior claim on the house He even appeared to harbor very little resentment

against the landlord who had let the place go The blame, he felt, lay on himself and his wife, and about equally so He was mildly self-reproachful and felt he had lost an unusual oppor tunity which there was no hope of regaining In short, he was

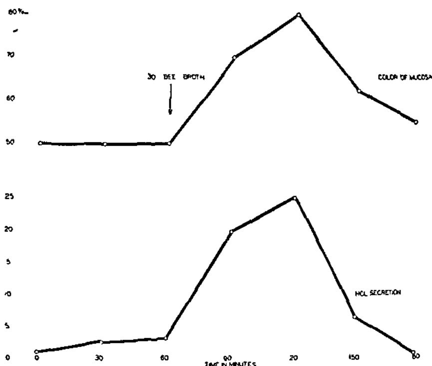


Fig 31a Usual response to ingestion of beef broth in terms of gastric function.

downcast and resigned, and there was no aggressiveness or fight' in him That morning 30 cc of beef broth had been introduced into his stoma

The curve in Fig 31a illustrates the usual response in terms of gastric acidity and vascularity to the ingestion of 30 cc of beef broth It will be seen that a marked acceleration of acid production and a corresponding increase in vascularity occurred Comparing this effect with the behavior of the stomach

in response to the same stimulus when the subject was depressed (Fig 31b), one sees that in association with such a mood an actual inhibition of secretion and vascularity occurred The increase in vascularity following ingestion of the beef broth was small and poorly sustained The rise in acidity was

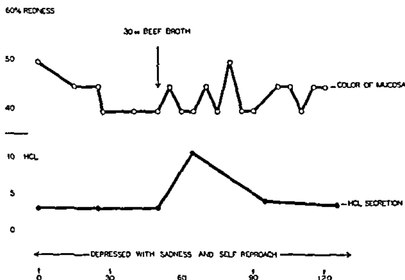


Fig 31b Inhibition of beef broth effect during sadness and self reproach.

brief and of the order of magnitude of a third of that observed during previous observations after a similar stimulus

Occurrence of Symptoms in Association with Gastric Hypofunction Anorexia and slight nausea were observed when pallor, decreased secretion of acid, and hypomotility were encountered in association with the emotional patterns described Pain, heartburn, distention were lacking at these times

4 *Resentment and Hostility* Aggressive feelings including resentment and hostility were found associated with a pattern

of gastric functioning entirely different from that associated with the emotions described above

A One opportunity to make such an observation occurred after our subject had spent the previous day in the out-patient department of the hospital having routine physical examination, blood studies, and x-rays He came to the laboratory red faced with anger and brimming over with feelings of resentment and hostility against a certain clinic secretary In addition, there was a strong element of humiliation in his attitude He had had to tolerate a good deal of 'running back and forth,' carrying various slips of paper, and other manner of 'red-tape' This he did not take altogether in good part He had come to look upon himself as a privileged character who should be immune to routine abuses Several times he had the impulse to quit the whole thing and return to the laboratory, but he stuck it out' At the completion of the studies, he was detained by the secretary of the last clinic he visited and was not permitted to return to the laboratory He remonstrated with her in vain She stubbornly refused to let him go With his further persuasive efforts the secretary became irritable and vindictive The patient, humiliated and strongly resentful, stood waiting in silence

The following morning, when he came to the laboratory bursting with resentment, we found his stomach in the condition in which we might expect to find it if he were about to devour a big meal 'I wish I could get my hands on her neck,' he said

Fig 32 illustrates the changes in gastric physiology which were associated with these dominant feelings The level of gastric secretion in terms of volume, acidity, and parietal cell output was three times normal In addition the mucous membrane was turgid, engorged, and much redder than usual For

the first half-hour we discussed the experience with him in an unsympathetic fashion and were able to increase his hostility and at the same time accentuate the effects observed in the stomach Then we attempted to divert him and were suc-

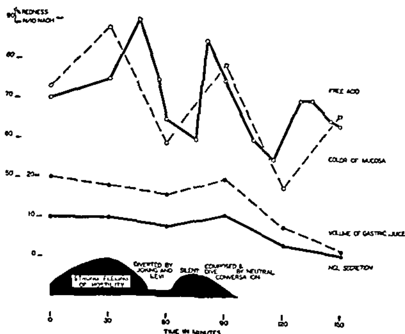


Fig 32 Changes in gastric physiology associated with feelings of hostility

cessful in a measure in relieving his hostile feelings and preventing a further rise in acidity The engorgement of the mucous membrane during this period subsided perceptibly After another 30 minutes we ran out of conversation and Tom lapsed into silence and brooded again over his wounds This recrudescence of hostile feelings was accompanied by a parallel vascular response with hyperaemia and engorgement of the stomach mucosa and also accelerated acid production Later we diverted him again, and this time were able to dispel

entirely his troublesome emotions This change in mood was accompanied by a return towards normal of the values for vascularity and acid secretion

B The associated changes in motor activity accompanying feelings of resentment and hostility were observed on another occasion A spontaneous phase of accelerated gastric activity had subsided an hour before and another would not be expected for at least one and one-half to two hours later The parietal secretion and blood flow had not quite fallen to their control level, although contractions had decreased nearly to a minimum with waves less than 1 cm high on the recorded tracing At this moment a doctor for whom Tom had been engaged to do piecework housecleaning after hours entered the room As he entered Tom flushed a little, because he resented the past attitude of that doctor towards his work The latter had insinuated that Tom's charges were excessive and that he worked too slowly The doctor came to pay him off and tell him that his services were no longer required Tom did not mind so much losing the work but he was angry and hostile about the aspersion cast upon his abilities and conscientiousness Reference to the previous chapter will indicate why such a topic would be to him an especially sensitive one He felt humiliated and resentful His face was red and his collar seemed too tight The gastric mucosa became hyperaemic and engorged and acid production more than doubled Vigorous contractions started and his stomach presented an appearance of overactivity similar to but less marked than that encountered in experimentally induced gastritis (Chapter IX) Fig 33 illustrates the changes diagrammatically

5 *Anxiety* Anxiety and the complex of conflicting feelings found to be associated with it were regularly accom-

panied by hyperaemia, hypersecretion and hypermotility of the stomach similar to that described above

A An illustrative example of such findings occurred on the day on which the subject's stepdaughter was to be cystoscoped

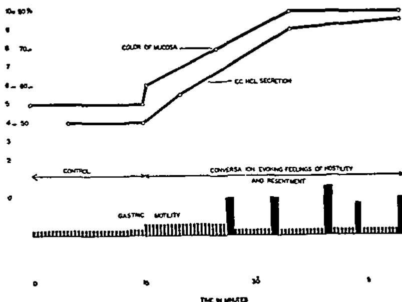


Fig 33 Increased motility accompanying hyperaemia and hyperacidity in association with hostility and resentment.

for a suspected carcinoma of the bladder He was overactive and talkative all morning and frequently expressed anxiety over what the findings would be on cystoscopy He was carefully questioned about associated feelings of shame guilt resentment etc, but anxiety seemed clearly to be the dominant affect Coupled with it were feelings of doubt and dread about the possible outcome The overactivity in the stomach persisted throughout three hours of observation The values were not as high as those encountered in the experiments involving

resentment detailed above, but neither did the emotion seem as intense

When anxiety was of short duration and could be completely dispelled, the accompanying changes in stomach function were also found to be evanescent

B One morning Tom was 15 minutes late and both the experimenter and the technician were three-quarters of an hour late in arriving at the laboratory The subject waited with restless anxiety accompanied by doubt and questionable feelings of guilt regarding the possibility of having misinterpreted orders It so happened that we had carried out some special studies in another laboratory in a remote part of the hospital the previous morning He worried about having been late and wondered whether or not he had been expected to appear in that other laboratory, and if so how he would find it He was greatly relieved when we arrived The changes in the stomach encountered on this day are recorded graphically in Fig 34 They consisted of hyperaemia and hyperacidity, which, however, persisted for only a half hour For the remainder of the morning the values were average

C The most marked alterations in gastric functions which were encountered were associated with anxiety provoked by our failure to inform the subject how long he might expect an income from the laboratory As recounted in the previous chapter, he had been receiving Government aid prior to his employment with us, and the rise in his family's standard of living since his new job had meant a great deal to him The subject of how long his job would last had come up in a discussion between himself and his wife the previous evening He decided to inquire about it the next morning Both he and his wife were so anxious about the answer, however, that neither of them slept at all The next morning the values

for vascularity and acidity were the highest encountered in any of the studies except after histamine stimulation As soon as he spoke of his problem he was reassured that he would be provided for indefinitely, but the changed behavior of the

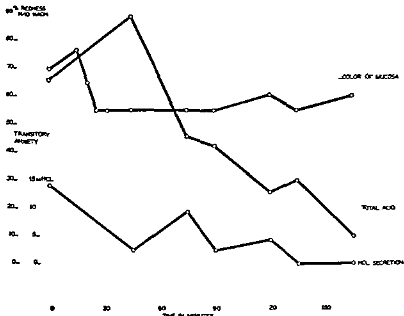


Fig 34 Changes in vascularity and acid secretion associated with transitory anxiety

stomach persisted until the experiment was concluded three hours later

6 *Prolonged Effects Associated with Sustained Emotional Tension* Sustained alterations in gastric function were also noted in association with more prolonged periods of emotional stress One striking experiment involved an observation which extended over five weeks Two of these weeks were marked by constant anxiety and punctuated with periods of doubt conflict, frustration, and resentment None of these

feelings was as intense or dramatic as those encountered in the experiments detailed above, but they seemed significant because of their long duration

The first 3 weeks comprised the control period during which the vascularity of the stomach averaged 46 and the output of acid 3 6 cc per hour These values corresponded approximately to the usual basal levels

Following this the situation which provoked the anxiety occurred Tom's stepdaughter's children were placed in a Catholic home by the officers of the surrogate's court because their mother was compelled to go to the hospital She had separated from the father, who was not competent to care for the children Our subject's wife preferred to take them home with her, but her daughter opposed the plan because it would relieve the children's father of financial responsibility If they were placed in the Catholic home she felt that the authorities would see to it that the father was sued for support Tom privately favored this latter plan because it would mean fewer mouths to feed Furthermore, his own daughter did not get on well with her stepbrothers and -sisters In the discussion, however, he supported his wife's stand in order to avoid domestic conflict and also because he still retained some ambivalence about the problem The youngest boy, next to his own daughter, was his particular 'pet He felt a special bond with him because his mother had partially rejected the child on the ground of his many resemblances to her estranged husband Tom had stepped in and become the boy's champion The little fellow frankly considered being deposited in the institution as tantamount to desertion, and Tom wanted to avoid any such appearance The court ruled that the children must be placed there, how-

ever Tom had lost his fight, but was relieved that the matter was settled During the two weeks of negotiation about this problem the average color of the mucosa was 53 and the average parietal cell output 5 1 cc per ½ hour These values

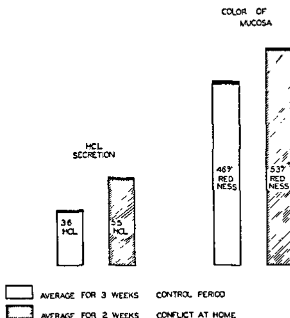


FIG 35 Sustained hyperfunction of the stomach during a period of prolonged anxiety

were roughly 20 per cent higher than those of the control period (Fig 35)

Several months later, since it was clear that the children would be happier at home despite the solicitous care of the orphanage, Tom determined to take them out and bring them to live with him A certain benefactor on whom Tom depended partially for livelihood heard about the plan and threatened to withdraw his support Tom persisted in his determination to undertake the additional responsibility of car-

ing for the children His reaction to this threat to his security was characterized by resentment at the interference with his personal affairs and seeming discrimination against him, and anxiety about his economic welfare

During this period of stress the average basal secretion of acid was significantly higher than during the preceding two weeks, and his membrane was continuously engorged and reddened

He was most eager to throw off his dependence on this person, and when a new source of revenue became available in the form of increased pay from the hospital, two weeks later, he did so with great relief Again his acid production and vascularity returned to former levels The changes are illustrated in Fig 36

Influence of Sleep Frequently the patient slept through much of an experimental period When gastric function was accelerated in a setting of emotional conflict sleeping did not appear to reduce it or modify it in any way Similarly when the stomach was pale and quiescent before sleep, it remained so during the sleep unless one of the transitory phases of spontaneously accelerated gastric function happened to occur at that time These occasionally began during sleep

Comment Certain observers[4] have noted further increase in gastric function during sleep which followed intense emotional conflict

Occurrence of Heartburn An annoying intermittent burning sensation felt beneath the region of the xiphoid, coming shortly after meals and persisting for an hour or two was a persistent complaint of Tom s during the two years of financial insecurity which preceded his coming to our laboratory A few weeks after becoming settled in his new job, the symptom stopped and recurred only at times of special stress

Abdominal Pain Migratory abdominal cramps of moderate intensity occurred at intervals when emotional conflict was present Occasionally these were associated with diarrhoea It

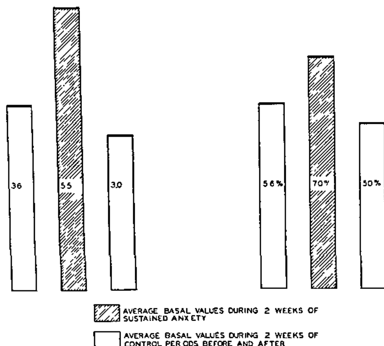


FIG 36 Sustained acceleration of gastric function during chronic emotional conflict.

will be noted in Chapter VIII that the sensitivity of the stomach to pain from vigorous contractions is increased at times of hyperaemia and engorgement

Secretion of Saliva The amount of salivary secretion during an experimental period was found to parallel roughly the volume of gastric juice secreted The average accumulation of saliva during the 3 hours of a 'control' morning was 40 cc

On the day when the effects of beef broth on the stomach were inhibited by his depressed mood, the salivary output was 10 cc On one day of intense resentment it was 72 and on the day marked by anxiety over the duration of his job it was 56 cc

Comment These findings are generally compatible with those of other investigators[5,6] who have studied salivary secretion in man during emotional stress Salivary secretion may parallel in some way the production of gastric mucus Increased output of saliva was observed under most conditions which were associated with increased secretion of gastric juice After histamine stimulation, however, which was regularly followed by a marked acceleration of acid secretion in the stomach and a comparatively insignificant increase in the output of mucus, salivary flow was not increased

Other Bodily Functions It has already been mentioned that the vasomotor alterations we have encountered in the stomach often corresponded to similar pallor and blushing of the face

In addition we observed correlations in the amount of talk*ing he did and in the general activity of the body* During periods marked by fear or depression he was relatively taciturn and inactive He showed a general paucity and slowness of movement During other periods of emotional stress characterized by anxiety and resentment, he was over-talkative, restless, and overactive His manner at these times often included an exaggerated heartiness

Appetite Despite the fact that under circumstances of anxiety and resentment the stomach of our subject was found *to be in a state of physiologic preparedness for food,* appetite was usually lacking and intake of food was thus usually greatly reduced

During three days which culminated in what he felt was

the avoidable death of his stepdaughter, he experienced intense anxiety and resentment against the apparently casual attitude of the doctors and their patronizing treatment of him Both Tom and his wife had anorexia, ate only two or three sandwiches and tea each day, and experienced diarrhoea with 5-6 watery stools a day but no cramps During this time despite the anorexia, gastric secretion of acid was active and the mucosa hyperaemic Two of the three nights Tom was awakened with burning of his abdominal wall by escaping secretion *Each time his bandages were saturated with gastric juice* and required changing

Comment This apparent dissociation of function is of special interest The stomach during the mixed emotional states described functions actively and becomes prepared for the digestion of food In certain instances the appetite fails however, and the subject does not wish to eat He may then even reject food This indicates clearly that the physiologic state of the stomach does not determine the presence or absence of appetite

Others have studied subjects who under circumstances of *intense anxiety and resentment* have an unusually large appetite and actually gorge themselves with food [4] It appears that the phenomenon of appetite may accompany the stomach's physiologic preparedness for food or it may not It may be that the acceptability of the emotion involved determines whether or not the proper association occurs If the hostility which he is experiencing is rejected and repressed by the individual, he may reject the food for which his stomach during this turmoil has become prepared

General Discussion From the above data it is clear that emotional stress may be associated with profound physiologic changes in the stomach as well as elsewhere in the body

It cannot be argued from our observations that the stomachs of all people would display such effects, but in our subject, at any rate, it may be said that emotions involving an attitude of fearsome shrinking or a desire for escape were accompanied by a depression of gastric function in terms of vascularity, acid production and motor activity. Confirmation of this finding exists in the work of Cannon[2] and others[7,9]. Emotions involving an aggressive attitude, on the other hand, were *found accompanied by an increase in vascularity, secretion,* and motility such as would be found as a prelude to the ingestion of food. This observation finds confirmation in the studies of Gordon and Chernya,[10] who found in a patient with a gastric fistula, who had had consistently a fasting free acidity in the low normal range, a sustained marked hyperacidity during a period of restlessness, homesickness, and resentment towards their experimental demands. Mittelmann and Wolff[4] studied the life histories of a group of patients with gastritis, duodenitis, and peptic ulcer. They found that symptoms were prominent during periods marked by experiences involving emotional conflicts and reactions of anxiety, hostility, and resentment. Bleeding from and perforation of peptic ulcers occurred at these times. When incidents in the patients' past lives which were associated with pronounced feelings of *insecurity were discussed in interviews in the laboratory,* acceleration of acid output and motor activity in the stomach were recorded. In certain normal controls, too, hyperacidity and hypermotility were found when emotional reactions involving hostility and resentment were induced. With reassurance and growing feelings of security, the hyperfunction in the stomach subsided.

The occurrence of hyperfunction of the stomach, in association with these distressing emotional states, has been con-

firmed in Tom In addition we have observed that the stomach mucosa becomes intensely red, engorged, and turgid at these times, presenting an aspect similar to that designated by gastroscopists as hypertrophic gastritis

The extent of the hypermotility, hypersecretion and hypervascularity has been shown to be roughly proportional to the intensity and duration of the emotions experienced Moreover, the duration of the changes appears to be governed by the length of time the unfavorable situation and consequent affective states last, since brief episodes of conflict and anxiety were associated with fleeting changes in the stomach, while conflict prolonged over a period of two weeks was associated with a more or less continuously elevated level of secretion, motility, and vascularity

Whether or not the hyperfunction of the stomach occurring with emotional conflicts involving anxiety, hostility and resentment depends upon or is accentuated by the suppression of expression of these feelings cannot be definitely deduced from the data given here Tom was not in a position to give expression to his feelings of hostility towards a member of the staff Any such act would have given rise to even more serious conflicts--guilty feelings and anxiety about endangering his job It seems likely, however that if giving expression to hostility would resolve the conflict and relieve the repressed feelings the hyperfunction of the stomach, too would subside, since the relief of tension by reassurance or diversion was found effective in decreasing gastric hyperfunction

Summary It has been shown that changing affective states are reflected in the stomach in the form of alterations in secretion motility, and vascularity Pleasurable thoughts of eating were accompanied by increase in all three of these functions So also were reactions and emotions involving conflict hos-

tility, resentment, and anxiety, when the subject had no notion of eating and, in fact, may have had actual distaste for food Fear, sadness, and other feelings involving a desire for withdrawal were found to be marked by a depression of these gastric functions It was noted that vascular changes in the face characterized by pallor or flushing regularly corresponded to similar changes in the stomach mucosa Also variations in talkativeness and general bodily activity were noted

Output of saliva, while it did not accurately parallel acid output in the stomach, did increase and decrease under the same circumstances, and the changes corresponded roughly to the changes in total volume of gastric juice

Conclusions Profound alterations in gastric function as well as in other bodily patterns were found to accompany emotional disturbances The alterations in gastric function fell into two categories (1) depression of acid output, motor activity, and vascularity, and (2) acceleration of these functions The former was associated with a reaction of flight or withdrawal from an emotionally charged situation The latter accompanied a reaction of internal conflict, with an unfulfilled desire for aggression and fighting back Profound and prolonged emotional disturbances of this kind were accompanied by marked and prolonged increases in gastric motility, secretion, and vascularity, with reddening and engorgement of the mucous membrane, often reproducing the picture of 'gastritis' (see Chapter IX)

BIBLIOGRAPHY

1 Beaumont, W *Experiments and observations on the gastric juice and the physiology of digestion*, F P Allen Plattsburg 1833
2 Cannon, W B 'The influence of emotional states on the functions of the alimentary canal *Am J Med Sci* 137 480 1909

3 Pavlov I *The work of the digestive glands* English translation from the Russian by W H Thompson C Griffin & Co London, 1910

4 Mittelmann B, and H G Wolff Emotions and gastroduodenal function Experimental studies on patients with gastritis duodenitis and peptic ulcer *Psychosomatic Med* 4 5 1942

5 Wittkower E Studies on the influence of the emotions on the functions of organs' *J Ment Sci* 81 533 1935

6 Strongin E I, and L E Hinsie Parotid gland secretions in manic-depressive patients *Am J Psychiat* 94 1459 1938

7 Bogen H Experimentelle Untersuchungen uber psychische und assoziative Magensaftsekretion beim Menschen, *Pflug Arch f d ges Physiol* 117 150 1907

8 Lavenson R S Observations on a child with a gastric fistula in relation to recent advances in the physiology of gastric digestion *Arch Int Med* 4 271 1909

9 Colombi, C and Sacchi J La secrezione psichica dello stomaco studiata in un uomo portatore di fistola gastrica *Arch d'Ist Biochim Ital* 3 263 Aug 1931

10 Gordon O L and Y M Chernya Physiology of the gastric secretion in man studies on patients with gastric fistula and artificial oesophagus *Klin Med* (No 12) 18 63 1940

Gastric Emptying Time

BEAUMONT[1] put a great many foods into the stomach of his subject and removed samples of the gastric content at intervals for examination He was interested not so much in the length of time food remained in the stomach as in what happened to the food and how long it took for the foods to disintegrate He did observe however that oily substances remained in the organ for a relatively long period of time Leafy vegetables remained longer than meats, and starches were the most rapidly evacuated

It has already been shown that emptying of the stomach depends upon the occurrence of vigorous contractions of the type illustrated in Chapter VI In addition we have demonstrated that these vigorous contractions occur only in the company of accelerated acid secretion and hyperaemia of the mucosa Therefore the duration of digestion in the stomach would be expected to be relatively long when gastric function is inhibited and short when it is enhanced

Studies of other investigators[2, 3] have shown that the composition of a meal influences greatly the length of time it remains in the stomach A nearly pure protein or carbohydrate

meal is quickly discharged, while the presence of fat in a meal generally prolongs the emptying time This retarding effect is due to the fact that the presence of fat in the duodenum causes the liberation of a hormone called enterogastrone[4] into the blood stream This material not only inhibits motility and thus delays gastric emptying, but its influence results in pallor of the mucosa and decreased acid output

On the basis of the data in the foregoing chapters, one would expect that wide variations in the duration of gastric digestion would occur during periods of emotional conflict This, indeed, has been shown to be the case by other workers,[5, 6] who found undigested food remaining in the stomach for more than 12 hours in the presence of fear and certain other emotions An unusual acceleration of digestion accompanying emotional stress would be less readily recognized, and, indeed, little has been suggested in that regard

Procedure Our subject was asked to eat a specific breakfast each morning between 6 00 and 6 30 and to appear at the laboratory at 9 00 A M After arrival he went about his activities of cleaning the laboratory, and then, at a time which was selected arbitrarily and which varied irregularly from day to day, his stoma was uncovered and the contents of his stomach examined After removal of the contents, the balloon and collection tubes were reinserted, and records of contractions acid secretion, and vascularity were made according to the methods described in Chapter II

Observations Average Breakfast At 6 30 A M the subject ate breakfast, which consisted of 2 eggs, scrambled in butter, 1 slice of buttered bread, 1 pint of milk, and 5 cups of weak coffee

At noon, 5½ hours later, the process of digestion was not completed 300 cc of greasy, very fluid, yellowish gruel, ap-

proximately 25 per cent of the bulk of the meal being recovered The stomach was not in a state of accelerated function The color of the mucosa was 60 Titratable free acid of the undigested material was 4 The pattern of contractions was different from that recorded at any time in the fasting stomach The waves came in groups of 3-5, the earliest waves in the groups being small, and each subsequent one higher, until they reached a size of about one-fourth that of the usual recorded vigorous contraction Occasionally there occurred a short period of quiescence followed by a similar group of waves A sample of this tracing is reproduced in Fig 37

As a rule, under circumstances of relative security and contentment, the average breakfast was emptied completely from the stomach in 6 hours

Average Breakfast Poor in Fat When the breakfast described above was eaten without butter or milk and with boiled eggs the stomach was found to be entirely empty of food four and three-quarters hours after its ingestion The organ was still intensely active however The mucosa was hyperaemic and engorged Free acid was 88, and tall waves of contraction were occurring (see Fig 37)

Average Breakfast with Added Fat When the breakfast detailed in the first experiment was eaten with 100 gm extra butter, 6 hours later 10 per cent of the meal still remained in the stomach The mucosa was pale, 45-50 Free acid was 23 No contractions except the familiar basal 3-a-minute waves, were taking place

Duration of Gastric Digestion under Circumstances of Anxiety and Resentment The average breakfast which contained approximately 50 gm of fat was ingested each morning during 3 weeks of emotional conflict involving anxiety and resentment He was disturbed over his economic state

because of having loaned money unwisely to an irresponsible person, over an administrative delay in raising his pay from the hospital, the rising cost of wartime living, and the pros-

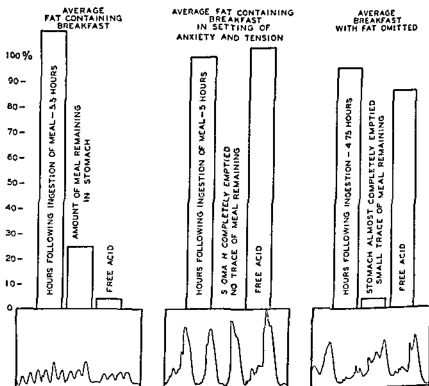


FIG 37 Duration of gastric digestion under various circumstances Motility pattern prevailing at the time the stomach was examined is represented in the lower frames.

pect of assuming new financial burdens with the support of his grandchildren

Throughout this period his stomach was found to be emptied entirely of his breakfast in 4-5 hours, although under circumstances of relative contentment complete emptying would not be expected for from 5-6 hours Furthermore, despite the presence of fat in the meal, his mucosa was hyperaemic, acid values were high, and motility active

On one occasion in the midst of this period he was entrusted with an errand which was obviously designed to test his eligibility for promotion to a more responsible job in the laboratory He was intensely eager to discharge his responsibility creditably, and in his anxiety was overactive, over-talkative, and perspired a good deal

His stomach was examined 5 hours after ingestion of breakfast The stomach was empty The mucosa was red (85), turgid, and engorged Free acid was 104, and motility was unusually active (see Fig 37)

Delayed Gastric Emptying Time Accompanying a Reaction of Fear Tom kept an appointment with a civil functionary one morning to apply for the privilege of adopting his step-grandchildren He had been told that the authority in question was exceedingly stern and inflexible Tom was afraid that he would be unable to give an articulate and convincing account of himself When he began to speak he found that his mouth was dry and his voice for a few moments was lost The officer was not as formidable as she had been described, however She quickly put Tom as his ease and a satisfactory settlement was arrived at

Six and a half hours after ingestion of the average fat-containing breakfast, 20 per cent of the meal remained in Tom's stomach This was an unusually prolonged emptying time an hour longer than the average shown in Fig 37 The mucosa was pale—50 Free acid was 60, and no vigorous contractions were occurring

Discussion These experiments confirm earlier findings[2-4] that fat with meals not only prolongs gastric emptying time, but also actually inhibits acid secretion and motility, so that the period of gastric hyperfunction which follows the inges-

tion of a meal is self-limited This effect may be accentuated if a reaction of fear prevails at the time

On the other hand, however, it is clear that during feelings of insecurity and anxiety, the effects may be reversed In the examples cited, the amount of fat in the average breakfast described above was ineffective in either delaying the emptying time or decreasing gastric hyperfunction

Thus, changes in gastric function accompanying emotional stress may outweigh in effect those chemically induced by the ingested food It will be recalled from one of the experiments described in the previous chapter that the inhibition of gastric function accompanying feelings of dejection and self-depreciation prevented, in part, the usual hyperaemia and acceleration of acid secretion and motility following ingestion of beef broth Here, on the other hand, we have seen that the usual inhibitory effect on gastric function of fat in a meal was partly offset by a stimulation occurring in conjunction with anxiety and resentment

Summary and Conclusion 1 Under circumstances of relative well-being and emotional security, the average breakfast used in these experiments was found to remain in the stomach approximately 6 hours The omission of fat from the breakfast may shorten the process by ⅓ Additional fat may prolong it

2 Towards the latter part of gastric digestion of a fat-containing meal, acid secretion and motility in the stomach were only moderately active The mucosa was only moderately hyperaemic The pattern of gastric contractions was peculiar and differed from that recorded from a fasting stomach

3 After a breakfast lacking in fat, emptying of the stomach was relatively rapid and the organ continued in a hyperfunctioning state

4 A similar set of circumstances occurred following inges-

tion of the usual fat-containing breakfast at times when the subject was experiencing marked anxiety and resentment

5 The vascular engorgement, hypersecretion, and hypermotility which occurred in the stomach in association with emotional conflict involving anxiety, hostility, and resentment persisted despite the ingestion of an average fat containing meal

6 On the other hand, the inhibitory effects of the ingestion of fat on gastric function were accentuated during fear

7 Therefore, what is known about the length of time food remains in the stomach must be re-evaluated in the light of the profound alterations which accompany altered emotional states

BIBLIOGRAPHY

1 Beaumont, W *Experiments and obser ations on the gastric juice and the physiology of digestion* F P Allen Plattsburg 1833
Beaumont W *Physiology of digestion with experiments on the gastric juice*, 2nd ed Chauncey Goodrich Burlington 1847

2 McSwiney B A and W R Spurrell The effect of fat on gastric motility *J Physiol* 84 41 1935

3 Quigley J P H J Zettleman and A C Ivy Analysis of the factors involved in gastric motor inhibition by fats *Amer J Physiol* 108 643 1934

4 Gray J S W B Bradley and A C Ivy On the preparation and biological assay of enterogastrone *Am J Physiol* 118 463 1937

5 Cannon W B The influence of emotional states on the functions of the alimentary canal *Am J Med Sci* 137 480 1909

6 Alvarez W C *An introduction to gastroenterology*, Hoeber N Y 1940

CHAPTER VIII

Sensation in the Stomach and the Mechanisms Underlying Gastric Symptoms

SEVERAL observers have made studies on sensation in the stomach[24] While many of their inferences are undoubtedly correct, the methods used were for the most part either indirect or non quantitative, and a clear-cut exposition of the sensibility of the stomach is therefore not available This is especially true with regard to hot and cold sensation in the stomach and its sensitivity to pain stimuli Because the gastric mucosa of our subject was peculiarly accessible by reason of his large fistula sensory studies were carried out

Before the basis of gastrointestinal complaints can be understood, it is necessary to establish the circumstances under which a subject is able to appreciate various stimuli applied to the stomach Because of its proximity a consideration of the cardiac end of the oesophagus is relevant to the study, and best pursued first

1 *The Mucosa of the Cardiac End of the Oesophagus* When fluid substances were introduced directly into the stomach through the fistula, it was possible for them to be-

come diffused to all portions of the organ, including the cardiac end of the oesophagus

Heartburn When 50 per cent and 95 per cent alcohol, 1 N hydrochloric acid, 0 1 N sodium hydroxide or 1-30 suspension of mustard were introduced into the cavity of the stomach, moderately intense burning pain was felt beneath the region of the xiphoid The sensation lasted 10-30 seconds and was described as identical to the familiar 'heartburn'

Comment Through the work of Jones[5] and others,[6] it appears to have been established that the sensation known as heartburn occurs by reason of a reflex constriction of the cardiac end of the oesophagus, resulting from the irritating effect on the mucosal surface of the solutions mentioned Excessive gastric acidity is probably the commonest stimulus which gives rise to the complaint

Nausea In addition, nausea frequently resulted when these substances were allowed access to the lower end of the oesophagus, while nausea never resulted from applying them solely to the folds of gastric mucosa

The occurrence of nausea appeared to depend upon the concentration of the various irritants and was thus roughly proportional to the intensity of the substernal burning

A slight sensation of warmth without nausea occurred after ingestion of alcohol in concentration of 10 per cent With higher concentrations the heartburn became more intense until nausea and vomiting occurred

2 *The Normal Gastric Mucosa Touch* Every accessible part of the stomach lining was stimulated by light touch with a blunt glass rod 5 mm in diameter The method of stimulation is illustrated diagrammatically in Fig 38 Nowhere in the normal mucosa was the sensation appreciated

Temperature A thin non-elastic balloon with a diameter of 10 cm was introduced into the stomach Care was exercised to keep it away from the lower end of the oesophagus Water of various temperatures was circulated through it Tempera-

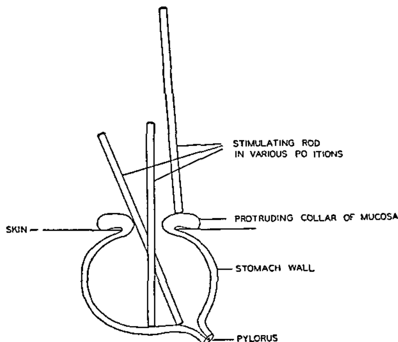


FIG. 38 Diagrammatic representation of the stomach wall with glass rod for touch and pressure

tures between 18° C and 40° C produced no sensation Outside that range the stimuli were appreciated appropriately as warm or cool and changes in temperature of 3° C or more were promptly and accurately recognized as warmer or cooler The sensations were felt deep in the epigastrium in an area about the size of a fist The latent period in recognizing a temperature stimulus was between 3 and 7 seconds The

apparatus used is illustrated in Fig 39 When the balloon was allowed to come into contact with the lower end of the oesophagus, the hot or cold sensation was of much greater intensity, occurred in the region beneath the xiphoid and completely overshadowed that arising from the stomach During gastroscopy when the light was allowed to touch the

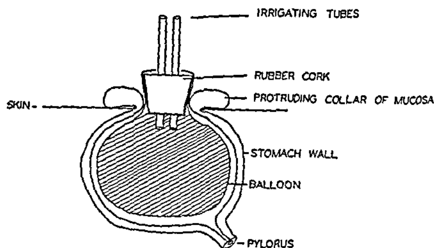


Fig 39 Diagram of the apparatus used to test temperature sensation in the stomach

stomach wall, the subject recognized a warm stimulus which he was able to localize very roughly on the correct side of the abdomen

Comment It is not possible to state certainly that these temperature stimuli were felt in the mucosa The latent period between the application and appreciation of the stimulus suggests that the end organs may lie somewhat deeper The fact that the warmth of the lamp in the gastroscopy was felt when it was applied to the posterior wall of the stomach indicates that the sensation actually arose from the organ and not by reason of transmission to the skin

Pressure The same glass rod used for testing touch was

applied more forcefully to the stomach wall Pressure was increased by attaching weights to the upper end of the glass rod When the lateral walls of the stomach were stimulated, the subject was rotated in order to keep the glass rod vertical Pressure of the order of 30 gm per sq cm evoked everywhere a sensation altogether similar to that recognized elsewhere on the body as pressure Only the roughest sort of localization was possible Usually the subject was only able to distinguish on which side of the body the stomach was being stimulated Separate stimuli had to be more than 9 cm apart to be distinguished

This sensation of pressure was also readily elicited in the collar of mucosa reflected on the abdominal wall which lacks the muscular and peritoneal coats Similarly, the sensation could be evoked by gently grasping a small fold of mucosa in the blades of a forceps Therefore, it seems likely that at least some pressure sensation arises from the mucosa

Pain A fold of normal mucosa held between the blades of a forceps was pinched tightly without inducing pain

Faradic stimuli strong enough to cause intense pain in the tongue failed to be painful when applied to the normal gastric mucosa

50 per cent 95 per cent alcohol, 1 N hydrochloric acid 0 1 N sodium hydroxide or 1-30 suspension of mustard when applied to folds of mucosa which were extruded through the stoma by having the patient increase his intra-abdominal pressure failed to cause pain

3 *Pain from the Deeper Layers of the Stomach Wall Effect of Vigorous Pressure* Vigorous pressure applied to the wall within the cavity of the stomach with the glass rod already described or other blunt objects caused pain The pain was of a steady, deep dull, gnawing nature It occurred ap-

proximately in the region of the stimulus Usually the subject could point a localization within 2-4 cm on the skin over the spot stimulated Increasing slightly the strength of the stimulus increased the intensity of the pain and usually induced an accompanying nausea

The average pressure necessary to induce pain was found to be 100 gm per sq cm The strength of stimulus required, however, was found to vary with the contractile state of the stomach and also with the degree of suddenness with which it was applied Pressures of small intensity (50 gm per sq cm) when applied suddenly were found to be painful when the stomach wall was strongly contracted When the wall was relatively relaxed, stimuli of greater intensity (150 gm per sq cm) were necessary to induce pain

When the stimulus was continuously applied, the pain persisted undiminished for 10-15 seconds and then gradually disappeared during the next 2 or 3 seconds As the pain decreased, it was possible to feel the relaxation of the stomach wall beneath the stimulating instrument Relaxation of the gastric wall after distention of the organ either with a balloon or a glass rod always occurred, whatever contractile state prevailed in the stomach at the time As a result of this phenomenon much greater force was required at any time in order to raise the intragastric pressure Occasionally the relaxation was followed by subsequent increase in the contractile state of the stomach wall, and under these circumstances the pain recurred When it did not recur spontaneously, the pain could be made to recur by adding 10-20 gm per sq cm to the pressure being applied

Effect of Distention A thin rubber balloon was introduced into the cavity of the stomach and inflated with air A feeling of fullness was regularly experienced when the intragastric

pressure rose to 15 mm of mercury as measured in a manometer of 7 mm inside diameter

It was necessary to introduce a relatively large amount of air, usually 600 cc, in order to raise the intragastric pressure to such a height, because each time the volume of air was increased there occurred a concomitant relaxation of the stomach wall as if the organ were adjusting itself to the larger volume Pain occurred when the pressure reached 35 mm of mercury and by this time the stomach regularly contained 1500 cc of air The pain was felt throughout the entire epigastrium and occasionally in the flanks and back at that level It was of a dull aching quality and was described by the subject as sickening,' since nausea was usually associated with it Increases in the contractile state of the stomach which occasionally followed distention lowered the strength of stimulus necessary to evoke this variety of pain in the same manner as that induced by pressure of a blunt object

As has been pointed out before the collar of stomach mucous membrane which is everted on the abdominal wall lacks the muscular and peritoneal coats Strong pressure on this area of stomach did not evoke pain It simply was recognized as a feeling of strong pressure

Comment During distention of the stomach with a balloon, obviously part of the force of the injected air was dissipated against the walls of the balloon while the remainder was transmitted to the walls of the stomach Since thin rubber condoms of uniform size were used in each instance in evaluating the results the distensibility of the balloon need not be considered as a variable factor, when the volume of air used remained the same

Painful Contractions Unusually vigorous contractions of the stomach were seen to produce the familiar 'pangs' of

hunger These pains were of a cramping nature, intermittent, lasting 10-40 seconds, deep, and of a moderate intensity, as a rule They were located about the umbilicus and below Usually the sensation was located deep in the left lower quadrant in an area 10 cm in diameter just above Poupart's ligament The 'threshold' pains occurred during contractions which raised the intragastric pressure to 30 mm of mercury as measured with an inlying balloon attached to a manometer 7 mm in cross section Nausea accompanied only the more intense of these pains

Comment Reference of the pain arising from gastric contractions to the left lower quadrant is not consistent with the findings of other workers (see [5]) Probably it is because of special circumstances in this case It might, for example, be related to the presence of peritoneal adhesions resulting from the old operation

Nausea Accompanying Pain Arising from Deeper Structures In general, the occurrence of nausea could be correlated with the intensity of the pain The more intense the pain, the more likely was nausea to accompany it Another factor which appeared to influence the occurrence of nausea, however, was the manner in which the pain was induced For example, nausea regularly occurred with a gnawing pain of relatively moderate intensity induced by pressure from a glass rod or distention with a balloon A cramp, resulting from a vigorous contraction of the stomach wall, had to be comparatively much more intense to induce nausea

Comment The fact that pain is induced by pressure from a blunt object on the wall within the cavity of the stomach, while such a stimulus applied to the protruding collar of mucosa, which lacks the muscular and peritoneal layers fails to induce pain, suggests that this variety of pain, like that

associated with distention of the organ with a balloon or with unusually vigorous contractions of the stomach wall, arises in the muscular or serosal coats of the stomach Deformation of sensory end organs in this region would presumably occur either from distention or strong contraction Since the strength of stimulus required to induce pain was smaller and the intensity of the pain greater when the stomach was tightly contracted it is improbable that pull on parietal peritoneum is responsible for the pain More likely the muscularis is the site of its origin Stretching of the peritoneal coat may be important with regard to nausea accompanying gastric pain since nausea was found to be much more in evidence with the pain which was induced by distention of the stomach wall either with a blunt object or balloon, than it was with that accompanying an unusually vigorous contraction

Lowered Pain Threshold with Mucosal Engorgement As pointed out above under ordinary circumstances it was necessary for a gastric contraction to raise the intragastric pressure to a height of at least 30 mm of mercury in order to be recognized as painful Under certain circumstances when gastric hyperfunction had been intense and sustained and the mucosa was markedly turgid and engorged, contractions which raised the intragastric pressure to only 20-25 mm of mercury were painful The character of the pain did not appear to differ from that already described as accompanying unusually vigorous contractions

Comment The reason for the lowered threshold for pain arising from the deeper structures when the mucosa is engorged is not clear It may be due either to the addition of a mucosal component to the pain, or to the occurrence of turgor and engorgement of the deeper layers accompanying that in the mucosa A similar lowering of threshold to burn-

ing pain in the forehead has been shown to obtain when the skin is erythematous [7]

4 *Pain Sensitivity in the Congested and Inflamed Gastric Mucosa* The application of strong irritants to the normal gastric mucosa, as pointed out above, did not induce pain (see p 145) Similarly, pinching and pricking and faradic stimuli, sufficient to evoke intense pain when tested on the skin, failed to induce pain when they were applied to the normal gastric mucosa

Tom recalled three occasions during his past life when his gastric mucosa had been tender and painful even to light touch The first was on the occasion of complete herniation of the stomach lining following an injury in a football game The membrane became cyanotic and oedematous and remained so for 3-4 hours Surgical intervention was finally necessary to accomplish reduction At this time Tom experienced an intense pain not unlike that following trauma to the testicles The pain persisted for 4-8 hours after reduction of the prolapsed organ Before reduction, the mucosa was markedly tender to the slightest digital pressure

The second episode of tenderness in the gastric mucosa followed repeated use of a coarse rubber tube on his funnel for feeding The mucosa lining the stoma became red and oedematous At this time, mere contact of the mucosa with the rubber tube was painful The sensation did not have the bright burning quality characteristic of the tenderness associated with a denuded area of skin It was of a duller nature, akin to that aroused by touching an abscess or deeper wound The tenderness persisted for 8 days after he discontinued use of the tube

The third episode of mucosal tenderness occurred during the operation in which Dr Donovan resected several buds of exu-

berant mucosal tissue that had appeared around the periphery of the exposed collar of mucosa and had given rise to profuse bleeding The areas were red and oedematous, and pinching them in a hemostat induced pain Detailed histological examination of one of these resected polyps revealed that it contained normal gastric mucosa except for acute inflammatory change characterized by infiltration of polymorphonuclear cells and a few round cells (see Fig 40)

Accordingly, we attempted to induce acute inflammation in an area of gastric mucosa which ordinarily lay within the cavity of the stomach but which was forced out through the stoma when the subject increased his intra abdominal pressure In order to eliminate the protective action of the mucus coating 1 N hydrochloric acid was allowed to fall on the mucosa at the rate of 12 drops a minute for 15 minutes Promptly the production of mucus was accelerated, soon it became cloudy and precipitated because of the high concentration of acid The mucus was aspirated away and powdered mustard was then applied directly to the mucosa The dropping of acid was continued in order to neutralize the newly formed mucus After half an hour, that portion of the mucosa which had been subjected to this procedure was intensely red boggy, and oedematous The control side was unchanged Both areas were then stimulated by pinching and faradic current As before no pain occurred in the control area but in the region rendered oedematous and inflamed intense pain occurred with the application of these stimuli

Comment The threshold for painful stimuli in the stomach may depend to a great extent on the condition diseased or otherwise, of the tissues We have shown that a contraction or other stimulus which does not elicit pain in the stomach under one set of circumstances may do so under another This

simple finding fits in well with the observations of Ivy[8] and others,[9, 10] and it probably explains the occurrence of abdominal discomfort and pain encountered so often in patients in association with gastric hyperfunctioning

In our experience, strong acid applied to the inflamed and even to the eroded mucosa was not painful Other workers have induced pain with acid,[11] and it appears likely that, to be painful, acid alone requires a further lowering of threshold than occurred with the degree of tissue damage we were able to study Contact of acid with the intensely inflamed and oedematous base of a large ulcer might well be painful, while lesser degrees of tissue change would require stronger stimuli, such as vigorous contractions, pinching, traction, or faradic current As pointed out above, even these stimuli failed to arouse pain from the normal mucosa

It has been inferred from other studies[12] that pain referable to the gastrointestinal tract can only arise from a *pull on the* mesentery or stimulus affecting the parietal peritoneum The observations recorded here do not lead to such a limited conclusion We have shown that stretching the visceral peritoneum without necessarily involving the parietal may result in pain, and that the peritoneal coat, visceral or parietal, need not be concerned in the production of pain in the stomach Certainly, pinching or applying faradic currents to an inflamed mucosa does not give rise to pain by stretching the visceral or parietal peritoneum

Referred Pain Most observers agree that gastric pains are referred to one of the upper quadrants of the abdomen often in the mid-epigastrium Our subject's stoma was located just in the mid-epigastrium, yet only painful sensations arising from the reflected collar of mucosa were felt at this site Usually, as pointed out above, Tom was able to point a locali-



A Ph t m cr graph f section f resected bud of gastric mucosa sh ing acute inflammat ry change



B Infiltration f p lym rphonucl ar and round cells among the tul ules of th astric gl nds

FIG 40

zation within 3-4 cm of the site of stimulation Distant reference occurred only when the pain arose from the whole circumference of the stomach, as in the case of distending the organ with a balloon or an unusually vigorous contraction Under these circumstances the pain was felt as has been mentioned, in the left lower quadrant just above Poupart's ligament. Cutaneous hyperaesthesia accompanying these abdominal pains was not noted

Summary and Conclusions Various sensory stimuli were applied to the wall within the cavity of the stomach as well as to a redundant fold of mucosa protruding through the stoma It was found that

1 Heartburn was due to stimulation of the mucosa lining the cardiac end of the oesophagus

2 Touch sensation was absent in the gastric mucosa

3 Pressure sensation was appreciated in the mucosa and roughly localized Two pressure points could be distinguished at distances of more than 9 cm

4 A warm stimulus above 40° C applied to the stomach mucosa was appreciated as heat, as was a cold stimulus below 18° C perceived as cold Between these limits no sensation was felt Outside the limits temperature differences of 3° C or more were distinguished Whether the sensation was felt in the mucosa or in the deeper layers was not established

5 Painful sensations could not be elicited by stimulation of the normal gastric mucosa With inflammation and oedema however, minor stimuli applied to the mucosa caused pain

6 Pain resulted from distention of the muscular and peritoneal coats of the stomach, either by pressure with a blunt object applied to the mucosa or by inflating a balloon within the viscus The pressure necessary to elicit pain regardless of the size of the area stimulated was of the order of 100 gm

per sq cm The strength of stimulus necessary to induce pain, and the intensity of the pain, however, were found to vary with the contractile state of the stomach and with the suddenness with which the stimulus was applied The more contracted the organ the more readily could pain be induced and the more intense it was Moreover, stimuli suddenly applied were more painful than those applied gradually

7 Unusually vigorous contractions of the stomach were found to induce pain Sensitivity to this pain was increased in the presence of hyperaemia and engorgement of the mucous membrane The more engorged the mucosa, the less forceful was the contraction necessary to induce pain

8 The *threshold for pain and therefore for the occurrence* of gastrointestinal symptoms varied with the condition of the tissues Vascular engorgement, inflammation, and oedema lowered the pain threshold and were therefore often associated with abdominal complaints

9 Nausea accompanied intense pain from whatever source and occurred most readily when the wall of the stomach was distended enough to put traction on the peritoneal coat

BIBLIOGRAPHY

1 Richet C Des proprietes chimiques et physiologiques du suc gastrique chez l homme et les animaux, Appendice A *Jour de l Anat et de la Physiol* 14 170 1878
2 Ross J On the segmental distribution of sensory disorders *Brain* 10 333 1888
3 Hertz A F The sensibility of the alimentary canal in health and disease *Lancet* 1 1051 1119 and 1187 1911
4 Mackenzie J *Symptoms and their interpretation*, Shaw and Sons London 1918
5 Jones C M *Digestive tract pain*, The Macmillan Co N Y 1938
6 Payne, W W and E P Poulton Experiments on visceral sen

sation Relation of pain to activity in the human oesophagus *J Physiol* 63 217 1927
7 Wolff H G J D Hardy, and H Goodell Unpublished data
Wolff H G and G A Schumacher *The influence of inflammation on the pain threshold of the skin in man* (In preparation)
8 Ivy A C (Quoted in Alvarez, W C *An introduction to gastroenterology*, Hoeber N Y 1940)
9 Kast L and S J Meltzer Die Sensibilitat der Bauchorgane' *Mitt a d Grenzgeb d Med v Chir* 19 586 1909
10 Kinsella V J The mechanism of pain production in abdominal visceral disease with special reference to the pains of peptic ulcer' *Med J Australia*, 15 (1) 64 1928
11 Palmer W L The mechanism of pain in gastric and in duodenal ulcer' *Arch Int Med* 39 109 Jan 1927
12 Lewis, T and J H Kellgren Observations relating to referred pain viscero motor reflexes and other associated phenomena *Clin Sci* 4 47 1939

CHAPTER IX

The Gastric Mucosa, 'Gastritis,' and Ulcer

SINCE the advent of gastroscopy there has been much interest in certain deviations from the usual appearance of the stomach mucosa called 'gastritis' The changes have been classified by various observers and morbid symptoms have been attributed to some of them[1,2]

Beaumont[4] was among the first to describe the clinical appearance of gastritis He called attention to unusual redness or pallor of the mucous membrane of St Martin's stomach, accompanied by small lesions which appeared pustular or more commonly grayish crusts which he called 'aphthous spots' His descriptions are not detailed enough to enable the present-day reader to visualize exactly what he saw In fact he usually noted merely that the stomach was of a 'morbid appearance and that most often after what he considered excessive eating or drinking of spiritous liquors on the part of his subject

The aphthous spots' which Beaumont noted have already been discussed in Chapter I, and it appears possible that he referred to flecks of rolled up precipitated mucus which adhered in places to the lining of the stomach

The occurrence of pustular lesions in the mucous membrane of the stomach has never been confirmed by subsequent observers and it is likely that in the face of the unsatisfactory lighting conditions and other difficulties of seeing clearly into his subject's stomach, Beaumont misinterpreted the appearance of *some of these mucous flecks as pustular* It is noteworthy that nowhere does he mention actually having recovered pus from one of them

As for the 'abnormal' redness or pallor of the mucosa which Beaumont observed, we have shown in the first chapter that profound color changes occur in the gastric mucosa in the absence of disease and in association with varying day-to-day conditions which must be regarded as normal

It appears, then, that there is some doubt whether color changes and localized spots on the stomach lining represent disease or 'gastritis,' or whether they should be looked upon as incidental variations within the range of 'normal'

This same question arises among gastroscopists today[57] There is much evidence to support the notion that small hemorrhagic lesions and so-called 'pigment spots,' regarded by *many as signs of disease,*[13] are in *reality artefacts due to the* trauma of the gastroscope itself or to the suction applied to the wall by the stomach tube in making the preliminary gastric analyses Ruffin,[8] for example, has shown that the application of suction through a Rehfuss tube in the process of obtaining gastric juice from the stomach sucked the mucosa against the holes in the tube and caused small submucosal and intra-mucosal hemorrhages After several minutes these spots became black and appeared identical to the lesions described by many as 'pigment spots'

Another change which has been considered of special significance in the diagnosis of gastritis is the size of the rugae

in the stomach as they appear through a gastroscope Ruffin[5] has shown that their size may be a function of the quantity of air used in inflating the organ to provide an adequate view With relatively large amounts of air, but not more than may be used during the course of ordinary gastroscopy, he found that the stomach lining could be flattened out entirely, so that it simulated the appearance of so-called atrophic gastritis We confirmed this finding but saw no blood vessels or other signs of atrophic gastritis

The Hyperfunctioning Stomach and 'Hypertrophic Gastritis' It has been pointed out in previous chapters that the hypersecreting stomach was always hyperaemic, turgid, engorged This was true whether the accelerated secretion occurred in response to the stimulus of food alcohol histamine, or to certain emotionally charged situations When such a state of engorgement and hyperfunction was intense and prolonged the gastric mucosa assumed the characteristics of what is known to gastroscopists as 'hypertrophic gastritis The folds became thick red, and succulent The slightest blow with the side of a glass rod, or stroking with a dry gauze resulted in the appearance of small hemorrhagic spots and erosions Frequently these minute hemorrhages occurred spontaneously, following vigorous contractions of the stomach wall The contractions themselves caused pain when they were of a sufficient magnitude, but not when the mucosa was pale and non-oedematous (see Chapter VIII) When this hyperfunctioning engorged condition of the stomach was prolonged in our subject he frequently complained of abdominal discomfort and pain

Comment It is clear from the account above that many of the signs of gastritis may be encountered in the normally functioning stomach or may be reproduced therein by minor

traumata associated with instrumentation To none of these changes discussed is the term gastritis altogether properly applied, since there was no indication that actual infiltration of inflammatory cells occurred The picture of hypertrophic gastritis, for example, was found to be induced by vasomotor changes resulting in hyperaemia and congestion of the mucosa These changes were often transitory, disappearing within an hour or two, a time too short for the subsidence of a true inflammatory process

The fact that the congested mucosa was especially susceptible to injury, however, suggested that vascular engorgement might predispose to the development and persistence of erosions and secondary inflammation Furthermore, sustained hyperaemia of the gastric mucosa assumes added significance, since it was found to be accompanied by symptoms of abdominal discomfort and pain

The Resting Gastric Mucosa In view of the special characteristics attributable to the mucosa during gastric hyperfunctioning, it seemed desirable to examine the behavior of the pallid resting gastric mucosa

Method The mucosa was examined after a fast of twelve or more hours In each case the stimuli were applied to folds of mucous membrane which ordinarily lay within the cavity of the stomach, but which were forced out through the stoma for the occasion by having the patient increase his intra abdominal pressure (see Fig 1, page 11) As noted in Chapter I, this region of the stomach lining was of altogether healthy appearance Many of the tests were also carried out on the collar of mucosa which always protruded through the stoma, and a few were made on remote parts of the stomach lining In the latter group observations of the membrane were made through a gastroscope

After observing and, in many instances, photographing the normal appearance of the mucous membrane, the stimulus was applied The area was then observed continuously for one hour Effects which persisted for a longer period were checked at intervals until they had disappeared

The stomach was allowed to rest for from two days to a week between these particular experiments, and they were undertaken only when the gastric mucosa appeared relatively pale and inactive

Observations Sudden Mechanical Trauma When the mucosa was struck a sharp blow with the side of a glass rod the area struck became blanched and depressed within one second It remained so from 1-5 seconds, depending on the force of the blow Following this there occurred a slight transitory hyperaemia in the same region which lasted for 3-10 seconds

Comment This effect has been observed before in dogs by others[9] who concluded that the trauma brought about a reflex contraction of the muscularis mucosae, which squeezed the blood from the mucosa for a few seconds

Continuous Mechanical Irritation For 15 minutes an area of 2 sq cm was rubbed gently with the blunt end of a glass rod Within 5 minutes the area had become slightly red and an obvious acceleration of mucus secretion had occurred The mucus was thick and transparent and clung tenaciously to the wall of the stomach A drop of Toepfer s solution allowed to fall on the region turned distinctly yellow indicating that its *p*H was higher than 4 3

Negative Pressure The stomach mucosa was sucked up against the hole in the side of a soft rubber catheter by the moderate negative pressure exerted by a 4 cm column of mercury for 1 minute At that point a small slightly elevated purpuric spot, the size of the hole in the tube appeared After

contact with the acid contents of the stomach for 15 minutes, the spot turned brown and then black. It thus had precisely the appearance of 'pigment spots' in the stomach described by gastroscopists. The force of the negative pressure which caused this lesion was far less than that usually applied with a syringe in the course of a routine gastric aspiration which regularly precedes gastroscopy.

In order to measure the force ordinarily applied during gastric analysis, the syringe was connected directly to a mercury U-tube manometer while a technician exerted the usual moderate tension on the plunger. The average negative pressure during 10 trials was 10 cm of mercury.

Abrasion of the Gastric Mucosa. The Protective Power of Mucus. Crystals of sodium chloride were sprinkled on the gastric mucosa and were then gently rubbed across its surface with the finger. Small linear hemorrhages were produced where the sharp crystals had scratched the surface. A prompt accumulation of mucus was observed in the injured area. The appearance of the stomach lining elsewhere was not changed and no extra mucus secretion was observed except in the injured area. Here the acceleration of mucus secretion was estimated at 3 to 6 fold. No local oedema or other evidences of inflammation were observed.

The following morning, approximately 24 hours later, all but a few of the larger lesions had disappeared. Here one saw a scale of opaque precipitated mucus adhering firmly to the injured area. Its surface was spotted with blackened blood pigment.

This lesion had precisely the appearance of what is spoken of by some gastroscopists as superficial gastritis.[3, 8]

Forty-eight hours after the lesion was inflicted, all evidence

of abnormality had disappeared This minor injury to the gastric mucosa was not accompanied by digestive complaints of any sort The patient ate two hours after it was inflicted, and subsequently at his usual intervals The stomach digested the food and emptied in the usual time

Effects of Chemical Trauma Acids and alkalis, drugs commonly taken by mouth, and condiments were applied directly to the stomach lining Each substance was rubbed very lightly on an area one centimeter square Another area of similar size, removed from the first site, was selected as a control This region was also rubbed lightly Both were observed continuously for an hour The reactions produced by irritating substances were classified in the following manner A slight erythema within the limits of the test area was called a 1+ reaction Moderate erythema within these limits was termed 2+ A 3+ was applied to erythema which extended beyond the one-centimeter square, and 4+ was used to indicate an inflammatory reaction extensive enough to cause evidences of oedema of the mucous membrane Below is a tabulation of the results obtained with the substances tested

Drug	*15 min.*	*hr*	*1 hr*
Alcohol 20 /	o	o	o
Alcohol 50 /	o	o	o
Alcohol 100,	o	o	o
Histamine 1 /	o	o	o
Acetyl salicylic acid (Powd. pill)	o	o	o
Sulfanilamide	o	o	o
Sulfapyridine	+	++	++
Sulfathiazole	o	o	o
Sulfaguanidine	o	o	o
Sulfadiazine	o	o	o
Ammonium chloride	o	o	o
Digitalis	o	o	o
Quinidine	o	o	o
Glucose 50,	o	o	o
Mustard (1 30 susp in water)	+	++	++
Hydrochloric acid 1 N	+	++	++
Sodium hydroxide 0 1 N	+	++	++

These same agents were similarly applied to an area on the volar surface of the forearm The 50 per cent and 100 per cent alcohol produced moderate local erythema The mustard, hydrochloric acid, and sodium hydroxide produced swelling, tenderness, and vesiculation in addition to erythema These effects were far more intense than the designated 4+ reaction

Comment The failure of strong irritants and corrosive agents to cause more than a slight-to-moderate erythema in the gastric mucosa, while they caused marked reaction with destruction of tissue when applied in similar concentration on the skin, is striking It indicates that the cells lining the stomach are endowed with some special protection against chemical injury The neighboring oesophagus is not so well protected It is well known that irritants brought into contact with the latter cause inflammation with pain and occasionally stricture

Presumably the special protection is afforded by the thick layer of tenacious mucus, which is adherent everywhere to the stomach lining and which is elaborated in increasing amounts in response to physical and chemical stimuli, thus protecting the membrane from significant injury

Properties of Mucus When a drop of Toepfer's solution was allowed to fall on the exposed collar of the mucous membrane or even on the stomach wall within the stoma, it failed to turn red until it came in contact with an accumulated pool of gastric juice When this test was made, a specimen had just been poured out containing 65 units of free acid, and all parts of the stomach wall including the exposed collar were moist with that secretion A drop of phenolphthalein was applied in like manner and this, too, failed to become red Thus it was concluded that the *p*H of the surface of the stomach wall lay between 4 and 7, although it contained a juice of less than *p*H 2

Thus the layer of mucus which clings everywhere to the stomach lining is sufficiently alkaline to maintain the surface of the gastric mucosa in a relatively neutral environment, despite the high concentration of acid in the gastric juice which it contains

In addition to its capacity to neutralize, mucus displayed another characteristic which makes it an effective insulator for the cells lining the stomach This was demonstrated in the following way

1 N hydrochloric acid was allowed to fall upon the gastric mucosa at the rate of 12 drops a minute At once the acceleration of the output of mucus was apparent, and the mucus which the drops of acid touched became gray and opaque This layer was pulled away with considerable difficulty from a small area The gray membranous flakes thus obtained were found to be relatively insoluble in gastric juice in 0 1 N hydrochloric acid and even in 1 0 N hydrochloric acid

To test this protective power an attempt was made to deprive a part of the gastric mucosa of its mucus covering and then to subject it to irritating stimuli

Production of Gastritis after the Removal of Covering of Mucus 1 0 N hydrochloric acid was allowed to fall upon the exposed gastric mucosa drop by drop as outlined above Within two minutes a thick layer of grayish opaque mucus had appeared over the area exposed to the acid The rate of application of the drops was increased from 12 to 20 a minute, while the accumulated mucus was sucked away through a pipette Within five minutes the mucosa beneath became moderately reddened and oedematous The 1-30 mustard suspension was then applied and its effect observed Within five minutes the redness and oedema were further accentuated and very minute bleeding points became evident as pin point black

These same agents were similarly applied to an area on the volar surface of the forearm The 50 per cent and 100 per cent alcohol produced moderate local erythema The mustard, hydrochloric acid, and sodium hydroxide produced swelling, tenderness, and vesiculation in addition to erythema These effects were far more intense than the designated 4+ reaction

Comment The failure of strong irritants and corrosive agents to cause more than a slight-to-moderate erythema in the gastric mucosa, while they caused marked reaction with destruction of tissue when applied in similar concentration on the skin, is striking It indicates that the cells lining the stomach are endowed with some special protection against chemical injury The neighboring oesophagus is not so well protected It is well known that irritants brought into contact with the latter cause inflammation with pain and occasionally stricture

Presumably the special protection is afforded by the thick layer of tenacious mucus, which is adherent everywhere to the stomach lining and which is elaborated in increasing amounts in response to physical and chemical stimuli, thus protecting the membrane from significant injury

Properties of Mucus When a drop of Toepfer's solution was allowed to fall on the exposed collar of the mucous membrane or even on the stomach wall within the stoma, it failed to turn red until it came in contact with an accumulated pool of gastric juice When this test was made, a specimen had just been poured out containing 65 units of free acid, and all parts of the stomach wall including the exposed collar were moist with that secretion A drop of phenolphthalein was applied in like manner and this, too, failed to become red Thus it was concluded that the *p*H of the surface of the stomach wall lay between 4 and 7, although it contained a juice of less than *p*H 2

this region A small erosion which occurred on this peripheral edge was exposed continuously to the digestive action of gastric juice for four days During the first 24 hours the denuded surface increased in size It bled intermittently At the end of

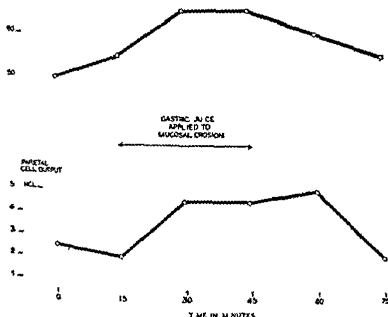


Fig 41 The acceleration of acid production following contact of gastric juice with an eroded mucosa

four days it exhibited the typical punched out appearance of a chronic peptic ulcer with well defined edges and a granulating base It measured approximately 4 mm in diameter 1 mm in depth and was growing rapidly (Fig 42d) Traction or pressure on this lesion resulted in pain of a dull gnawing character which was localized in the region of the lesion itself Throughout the four day period the whole mucosa was relatively engorged and the rate of acid secretion was significantly elevated

specks on the mucosa where drops of hemoglobin had been altered by the hydrochloric acid present

Mechanical traumata were also applied to the gastric mucosa in its state of induced inflammation A sharp blow with a glass rod which formerly resulted in a transitory blanching and subsequent reactive hyperaemia now induced minute bleeding points Rubbing with the blunt end of a glass rod also caused haemorrhage, and, as pointed out in Chapter II, these mechanical stimuli applied to such an area caused pain

Acceleration of Acid Output by Contact of Gastric Juice with Minute Erosions Two of the small hemorrhagic lesions described in the preceding paragraph were kept in contact with gastric juice with a titratable total acid of 90 for half an hour Mucus accumulated rapidly in the region, but it was removed at frequent intervals by suction through a small glass tube, and the acid gastric juice was then reapplied to the bare mucosa A sharp acceleration of acid secretion and concomitant hyperaemia of the whole stomach mucosa occurred and persisted for half an hour after the submersion of the haemorrhagic lesions was discontinued (Fig 41)

Comment In this phenomenon may lie an explanation of the persistent hyperacidity regularly encountered in persons suffering from gastritis and peptic ulcer The fact that the base of the ulcerated lesion which is constantly bathed in acid gastric juice effects a stimulation of acid secretion indicates that afferent impulses subserve this reflex without sensation resulting It is likely, however, that pain would follow an adequate chemical stimulus[10]

The Effect of Gastric Juice on an Area of Mucosa Lacking in Mucus The most peripheral edge of the collar of mucosa which lay exposed on the abdominal wall lacked adequate protection owing to defective formation of mucus in



A Normal Mucosal Fold during circumstances o[f] se[c]urity and contentment (Approx actual size)



B Same fold during hyperaemia and engorgement of gastric [m]u[c]osa associated with emotional con[f]lict involving [f]rustration and resentment (Approx actual size)



C Small mucosal erosion covered by blood stained flake of opaque mucus occurring in engorged hyperactive stomach (Approx actual size)





D Small punched-out ulceration induced by the [illegible] of gastric juice on an area [illegible] protected by mu[illegible] (Approx actual size)

E Dr[illegible] of ulcer (of D) enlarged approximately [illegible] times

Fig 4[illegible]

At the end of four days because of the hazard to the subject it was felt that the experiment could not be allowed to continue

The ulcer and surrounding area were covered with a protective petrolatum dressing Within three days, complete healing had taken place, leaving no trace of the lesion behind

Discussion It is clear that gastric juice is quite capable of attacking and digesting the mucous membrane of the stomach It does not do so under normal circumstances because it does not gain access to it Neither do other irritating and corrosive substances, taken as articles of diet, because the lining of the stomach is normally covered by an efficient insulation in the form of a protective covering of tenacious, viscous, alkaline mucus The latter combines with the acid in its immediate vicinity and thus maintains the cells of the gastric mucosa in a relatively neutral chemical environment It effectively diverts the force of any mechanical trauma or abrasive which may brush by, by presenting a slimy, mucinous surface Finally, in the presence of strong acid it precipitates and forms a relatively insoluble membranous shell over the delicate mucosal cells Once the protective powers of mucus are overcome, however, and the digestive juices have attacked and eroded the surface of the mucous membrane, a vicious cycle is set up, since the acid gastric juice in contact with a denuded region induces further acid secretion

Chronic ulceration then results from the interplay of protective and destructive forces If a minor erosion can be effectively covered with mucus and the hyperfunction of the stomach subsides spontaneously or can be made to subside by the ingestion of fat or the administration of drugs, healing takes place quickly and uneventfully If, on the other hand, hyperaemia and hypersecretion are sustained by a stimulus



A Normal Mucosal Fold during circumstances of security and contentment (Approx actual size)



B Same folds during hyperaemia and engorgement of gastric mucosa associated with emotional conflict involving hostility and resentment (Approx actual size)



C Small mucosal erosion covered by blood stained flake of opaque mucus occurring in engorged hyperactive stomach (Approx actual size)





D Small punched-out ulceration induced by the action of gastric juice on an area inadequately protected by mucus (Approx actual size)

E Drawing of ulcer (of D) enlarged approximately [illegible] times

Fig 4

which overwhelms the inhibitory influence of fat or drugs, the susceptibility of the mucosa to injury is enhanced and tissue damage proceeds unchecked, resulting in ulceration

Summary The healthy gastric mucosa varied in appearance within a wide range When the rate of acid production by the parietal cells was relatively slow, the mucosa was always comparatively pale and in this state relatively resistant to injury unless the continuity of its protective covering mucus was interrupted

Accelerated acid production and motor activity were always accompanied by hyperaemia and engorgement of the mucosa When vascular engorgement was prolonged the rugae became intensely red thick, and turgid, presenting the picture of what has been called hypertrophic gastritis In this state the mucosa was unusually fragile haemorrhages and small erosions resulting from even the most minor traumata Lowering of the pain threshold occurred and symptoms were often associated with this condition Thus the difference between hyperfunction in the stomach and hypertrophic gastritis was seen to be mainly one of degree Continued exposure of a small erosion to the digestive action of gastric juice for four days resulted in a peptic ulcer

Conclusions 1 Undue and prolonged acceleration of acid secretion in the stomach however provoked resulted in hyperaemia and engorgement of the mucous membrane resembling hypertrophic gastritis

2 The mucosa in this state was unusually susceptible to injury and even the most trifling traumata resulted in haemorrhages and small erosions

3 Ordinarily the mucosa was protected from injury by an effective coating of mucus Loss of this protection in the face

of minor traumata led to oedema, inflammatory changes, erosions, and haemorrhages

4 Contact of acid gastric juice with a denuded surface induced further hyperaemia and acceleration of acid secretion

5 Prolonged contact of acid gastric juice with a minor erosion resulted in the formation of a peptic ulcer

BIBLIOGRAPHY

1 Schindler, R M Ortmayer, and J F Renshaw 'Chronic gastritis *J A M A* 108 465, 1937

2 Carey J B The symptomatology of gastritis' *Am J Dig Dis & Nutr* 5 353 1938

3 McClure C W, F N Sweetsir, and I R Jankelson Chronic gastritis Gastroscopic and clinical study' *N E J Med* 225 259 1941

4 Beaumont, W *Experiments and observations on the gastric juice and the physiology of digestion* F P Allen Plattsburg, 1833

5 Ruffin J M and I W Brown The effect of inflation of the stomach upon the gastroscopic picture, *Am J Dig Dis* 7 418 1940

6 Ruffin J M and I W Brown Jr The occurrence of gastritis as diagnosed by gastroscopy in gastric neuroses *Am J Dig Dis* 7 414 1940

7 Howard J T and L Martin The gastritis problem, *South Med J* 34 921 1941

8 Ruffin J M Data in Press

9 Drury A N, H Florey and M E Florey The vascular reactions of the colonic mucosa of the dog to fright *J Physiol* 68 173 1929

10 Palmer W L The mechanism of pain in gastric and in duodenal ulcer *Arch Int Med* 39 109 Jan 1927

CHAPTER X

Formulation

It is clear from the foregoing chapters that a very wide variation in gastric function is compatible with good health Unlike the heart, lungs liver, and kidneys, the stomach is not called upon to work incessantly at a relatively high rate of activity It is subject to periodic phases of intense activity on the one hand and relative quiescence on the other

Alterations in gastric function may occur in response to a very large number of stimuli In the case of drugs and other physical and chemical agents, however the usual effects may be profoundly modified or even reversed by changes associated with the situation in which the subject finds himself and his reaction to it Furthermore it is important to note that reactions to the various stimuli are not confined to the stomach Other bodily changes occur as well When situational factors for example caused hyperaemia hypermotility and hyperacidity in the stomach, our subject showed associated vasomotor changes in the face, changes in mood general muscular activity and behavior The altered gastric function was merely a part of the whole pattern of bodily reaction

These functional alterations in the stomach assume special

importance, however, since it has been shown that when sustained they may lead to the occurrence of distressing symptoms and even to structural damage

To bring about the changes in gastric function accompanying various emotional states, adequate neural pathways exist Cannon has suggested that social inhibition of hostile action and consequent repressed conflict may give rise to 'positive inductance'—a physiological phenomenon described by Sherrington and Pavlov in which inhibition of a reaction is followed by a greater reaction than before It is well illustrated by the effect of an inhibitory stimulus on salivary secretion When a uniform conditioned stimulus has been causing a fairly uniform outflow of saliva, interference by a stimulus which inhibits the flow is followed by a greater efficacy of the conditioned stimulus This positive induction of activity may manifest itself also in restlessness and vocalization, as noted in the patient when aroused and frustrated (see p 126), and as is often seen when a dog is chained or confined

It is not possible with the evidence at hand to attribute the pattern of bodily changes observed solely to vagus or to sympathetic activity It seems more profitable at present to consider gastric changes which accompany emotional disturbances as part of a general bodily reaction pattern

The settings in which perversion of gastric functioning of the nature of hyperaemia, hypermotility and hypersecretion occurs have been noted, both in this study and in others, to comprise situations which offer a threat to the emotional security of the individual This state of the stomach is in fact the state of sustained readiness for eating It has been suggested[1] that it becomes associated with attempts to gain security in two ways through the coupling of eating with hostile aggression and of eating with the wish for dependence

and being cared for Side by side were found in subjects, on the one hand, desperate attempts to gain security by effective aggression, and on the other hand, efforts towards being cared for towards winning approval and at seeking unquestioning love Sometimes, one method prevailed, sometimes the other, but at all times there was conflict between them In any event, when situations bolster the emotional security of the individual, the overactivity of his stomach subsides, and symptoms abate

In the light of recorded facts the objectives in the management of patients who exhibit the gastritis and ulcer syndrome are clear Therapeutic efforts should be directed towards preventing or controlling gastric hyperfunction, and the problem resolves itself into one of the care of the man rather than merely his stomach

The agents and methods ordinarily in use, such as atropine, alkalis, and frequent feedings of milk and cream are directed towards the accomplishment of this objective The shortcomings of atropine have been discussed The drug inhibits the secretion of mucus as much or more than it does the secretion of hydrochloric acid, so the concentration of acid in the stomach remains the same or becomes slightly higher Atropine does effectively reduce motor activity, however and is often useful because of that Alkalis may relieve heartburn by lowering the acidity of the gastric content, which comes in contact with the mucosa of the cardiac end of the oesophagus The pains of ulcer, too, may be relieved by the temporary interruption of motor activity which is effected (Chapter III) and by the removal of the irritating influence which excessive acidity may exert The alkalis do not reduce gastric hyperfunctioning however, and when vigorous contractions are resumed following their ingestion the alkalis are rapidly flushed

through the pylorus, leaving the stomach in its former state Cream is perhaps the most effective agent, but, as we have shown, it is effective only in part in reducing the overactivity of the stomach which accompanies intense anxiety and conflict

It is well known that removal to the neutral yet constructive environment of a hospital is regularly beneficial to ulcer patients In fact, merely establishing a satisfactory relationship with a physician and being put on almost any regime helps The factors responsible for such improvement deserve close scrutiny

Consulting a physician and placing reliance on him gives the patient the conviction that he is being 'backed up,' and his feelings of being caught, of being alone, or of frustration are mitigated Furthermore, his reliance on the physician lessens the additional threat which merely being ill offers the patient's security At the first sign of improvement from a regime of alkalis and cream, his horizon appears brighter The hyperaemia and engorgement of his mucosa related to his reaction are reduced Pain and tissue damage occur less readily The chain has been broken If one can prevent new links from being forged, the patient continues to improve

To accomplish this step effectively it would be necessary, of course, to understand the dynamic factors which have contributed to the development of this reaction pattern of perverted gastric functioning Proper therapy, then, would involve the management of personality disorder, the consideration of which does not fall within the scope of this work The subject has been reviewed however, elsewhere, together with the social and economic implications of the increasing incidence of peptic ulcer in the male population [1]

It is to be hoped that the factors of emotional conflict, on

the one hand and security on the other, will be more directly dealt with in the future When they are, the error will be made less often of attributing specific curative effects to a particular surgical dietary, or chemo therapeutic measure the use of which happens to correspond in point of time to the regaining of self-confidence by the patient Dealing actively with the patient s life situation and his reactions to it may then be adequately judged as a means for the control of 'dyspepsia,' gastritis and peptic ulcer

BIBLIOGRAPHY

1 Mittelmann B and H G Wolff Emotions and gastroduodenal function. Experimental studies on patients with gastritis, duodenitis and peptic ulcer *Psychosomatic Med*, 4 5 1942

Appendix

Historical note on Gastric Fistula As early as 1530 there was reported a patient who acquired a hole in his stomach, which communicated with the outside world through the abdominal wall Matthew Cornax,[1] Professor of Medicine at the University of Vienna and Physician to Emperor Ferdinand I of Austria, wrote of a Bohemian peasant who, while hunting, was bitten in the abdomen by a snake He developed a gastric fistula and survived with it for 'a number of years' Later on, other isolated cases appeared Cornax and the others reported no studies on their patients

In 1825, William Beaumont[2] began experiments on Alexis St Martin, a French-Canadian voyageur, who three years before had acquired a gastric fistula as a result of an accidental shotgun wound in the abdomen The accident occurred when St Martin was 19, and he lived with his gastric fistula approximately an inch in diameter, until the age of 78 In fact he outlived Beaumont, and following the death of the latter, another physician, Francis Gurney Smith of Philadelphia studied Alexis St Martin further Smith was unable to add perceptibly to Beaumont's results, in fact he[3] contradicted Beaumont's finding of hydrochloric acid as the principal acid of the gastric juice contending that it existed only in negli-

gible amounts and that lactic acid was the physiologically important one Beaumont's work was later confirmed and Smith's publication forgotten

Alexis St Martin's survival after his accident for about 60 years demonstrated that a gastric fistula is no obstacle to longevity[4] He did not feed himself through his fistula, however, and it was not until 42 years after Beaumont's publication in 1833 that patients began to do so As early as 1875, a successful surgical gastrostomy was performed on a patient with obstructive carcinoma of the oesophagus[5] Although the palliative operation was successful, the patient died shortly thereafter of bronchopneumonia The following year (1876) another successful surgical gastrostomy was reported[6] This patient had acquired a benign stricture of the oesophagus after having swallowed lye Following operation he survived, free of gastrointestinal complaints, to be studied and reported two years later by Richet[7] Richet confirmed many of Beaumont's findings and added a few of his own His patient, unlike St Martin, actually fed himself through his fistula He poured the food in directly through a rubber tube without taking it into his mouth Eating in this fashion he gained 5 kg in weight during the 6 months following operation He observed that escaping gastric juice caused severe burning pain when it came in contact with the denuded edges of the skin immediately surrounding the stoma Richet looked inside and saw a pink undulating surface dotted with tiny bright holes which he, like Beaumont, took to be orifices of glands He investigated the sensibility of the mucosa and concluded that it did not appreciate touch, that introducing cold fluids evoked a painful sensation, and that alcohol elicited a sensation of heat The patient could not tell whether his stomach was full or empty

Very rapid filling or emptying of the stomach, however, was regularly associated with hiccough

Approximately 25 years after the publication of these studies, Pavlov [8] adapted the fistula technic to the study of gastric physiology in dogs In fact, he separated surgically a portion of the stomach from the rest of the organ so that nothing from the oesophagus or duodenum could gain access to it The blind pouch was connected to the abdominal wall by an artificial stoma Thus Pavlov was enabled to collect pure gastric juice free from contamination with food, saliva, or duodenal regurgitation and without the possibility of loss through the pylorus This surgically produced gastric pouch has since been known as the 'Pavlov pouch

Approximately 90 years after Beaumont's, 35 years after Richet s and 10 years after *Pavlov s observations, Carlson* [9] made studies on a patient with a gastric fistula half an inch in diameter He concerned himself largely with motor mechanisms and hunger contractions in particular He made one observation however, on vascularity namely, that strong contractions of the stomach were associated with increased redness of the mucous membrane On secretion, he made several observations, the most striking of which was that the resting fasting stomach secretes acid gastric juice This observation was contrary to the findings of Beaumont [2] and Pavlov,[8] who held that in the absence of stimuli, mechanical or chemical the stomach remained empty and failed to secrete Carlson s patient lived on for years serving alternately as experimental subject and diener in the laboratory, feeding himself through his stoma and enjoying good health free from gastrointestinal complaints

In 1936 Rouhier and Soupault [10] *reported the case of a patient* who had lived over 40 years in good health feeding her-

self through her fistula Numerous other patients with successfully functioning gastrostomies have been reported,[12,13] and there have been studies on the alterations of gastric physiology by gastrostomy

King[14] reviewed a large number of cases from his own practice and found that all of them showed a marked diminution of gastric acidity and in most instances an achlorhydria Nearly all of his operations, however, were done for cancer in the oesophagus Some of these neoplasms may have involved the stomach, and the achlorhydria may have been explained on that basis All the patients had rubber tubes fixed permanently in place in the stoma, and at autopsy their stomachs showed varying degrees of gastritis, which may have explained the achlorhydria in some of them

Cade and Latarjet[15] had the opportunity of studying a patient who acquired in infancy an epigastric hernia This contained a portion of the stomach, which became incarcerated with eventual separation of the mucosal surfaces of the pouch and the main stomach Later the anterior aspect of the pouch ulcerated through to the outside, and the patient was left with a spontaneously produced 'Pavlov pouch' These investigators confirmed Pavlov's work on animals in regard to secretion in the pouch in response to food taken into the main stomach, and in response to 'psychic' stimuli in the form of discussion of appetizing dishes[8] No note was made of changes in vascularity or color changes in the exposed mucous membrane

In 1907, Kaznelson[16] was able to confirm Pavlov's sham-feeding experiments on a human being who had an oesophageal as well as a gastric fistula

'Psychic' stimuli to gastric secretion as well as other aspects of gastric fistulae have been the subject of numerous investigations[11, 17, 18] The studies, however, were fragmentary because

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12 Petrowic, A A Beobachtungen an zwei gastrostomierten Kranken,' *Arch f verdauungskr* 52 297, 1932
13 Gordon, O L, and Y M Chernya 'Physiology of the gastric secretion in man, studies on patients with gastric fistula and artificial oesophagus' *Klin Med* (No 12) 18 63 1940
14 King, E S J Some reflections on gastrostomy, *Brit J Surg* 24 749, 1937
15 Cade A and A Latarjet 'Réalisation pathologique du petit estomac de Pavlov Etude physiologique et histologique,' *J de Physiol et de Path Gen* 7 221, 1905
16 Kaznelson H Scheinfutterungsversuche am Erwachsenen Menschen *Pflug Arch f d ges Physiol* 118 327 1907
17 Bogen H Experimentelle Untersuchungen uber psychische und assoziative Magensaftsekretion beim Menschen, *Pflug Arch f d ges Physiol* 117 150 1907
18 Colombi, C, and U Sacchi 'La secrezione psichica dello stomaco studiata in un uomo portatore di fistola gastrica, *Arch d Ist Biochim Ital* 3 263, Aug 1931
19 Hertz R and S Sterling Untersuchung uber den psychischen Magensaft bei einen Kranken nach Gastrostomie' *Deutsche Med Woch* Leipz v Berlin 36 1441, 1910